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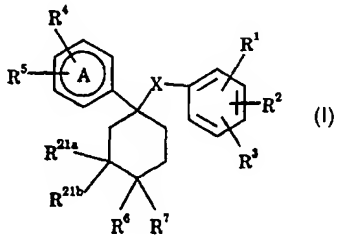
(54) Title: CYCLOHEXYL DERIVATIVES AND THEIR USE AS THERAPEUTIC AGENTS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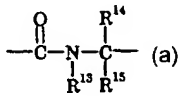
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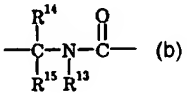
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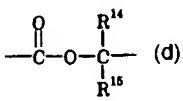
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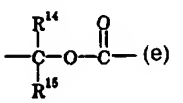
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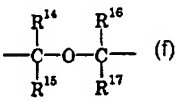
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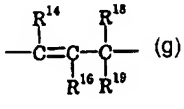
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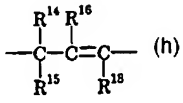
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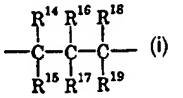
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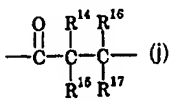
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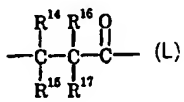
(k)


(L)

(57) Abstract: The present invention relates compounds of the formula (I): wherein ring A is a phenyl or pyridyl ring; X represents a linker selected from the group consisting of: (a), (b), (c), (d), (e), (f), (g), (h), (i), (j), (k), (l) and R^1, R^2, R^3,R^4, R^5, R^6, R^7, R^{13}, R^{14}, R^{15}, R^{16}, R?17, R^{18}, R^{19}, R^{21a} and R^{21b} are as defined herein. The compounds are of particular use in the treatment or prevention of depression, anxiety, pain, inflammation, migraine, emesis or postherpetic neuralgia.

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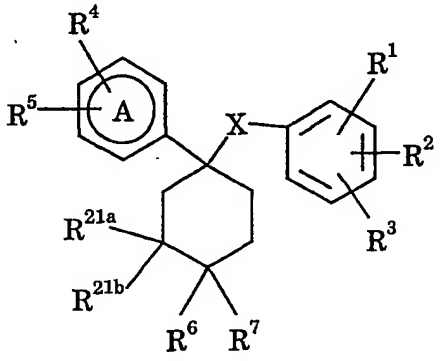
CYCLOHEXANE DERIVATIVES AND THEIR USE AS THERAPEUTIC AGENTS

This invention relates to a class of gem-disubstituted cyclohexane derivatives which are useful as tachykinin antagonists. More particularly, the compounds of the invention are useful as neurokinin 1 (NK-1) receptor antagonists.

The present invention provides compounds of the formula (I):

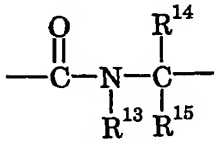


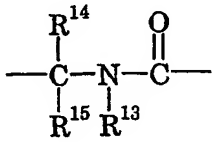
(I)

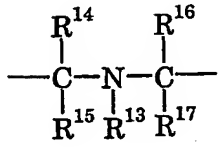
wherein

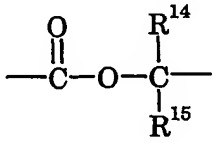
ring A is a phenyl or pyridyl ring;

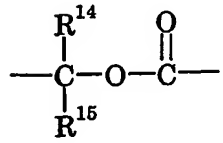
X represents a linker selected from the group consisting of:

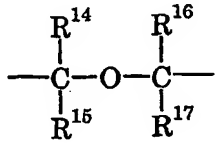
(a)  ,

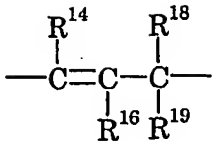
(b)  ,

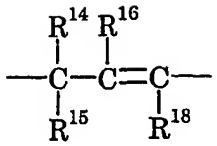
(c)  ,

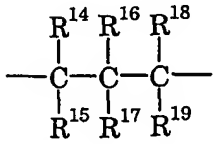
(d)  ,

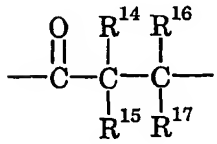
(e)  ,

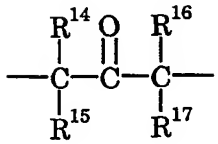
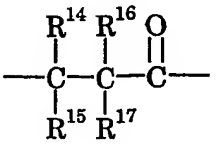
(f)  ,

(g)  ,

(h)  ,

(i)  ,

(j)  ,

(k)  , and (l)  ;

R^1 represents hydroxy, C_{1-6}alkyl, fluoroC_{1-6}alkyl, C_{2-6}alkenyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-4}alkyl, C_{1-6}alkoxyC_{1-4}alkoxy, fluoroC_{1-6}alkoxyC_{1-4}alkyl, C_{2-6}alkenyloxy, C_{3-7}cycloalkoxy, C_{3-7}cycloalkylC_{1-4}alkoxy, phenoxy, cyano, halogen, NR^aR^b, SR^a, SOR^a, SO_2R^a, OSO_2R^a, NR^aCOR^c, COR^a, CO_2R^a or $CONR^aR^b$ where R^a and R^b each independently represent hydrogen, C_{1-4}alkyl, C_{3-5}cycloalkyl, fluoroC_{1-4}alkyl or $CH_2CO_2C_{1-4}$alkyl, and R^c represents C_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkyl or phenyl;

R^2 represents hydrogen, halogen, C_{1-6}alkyl or C_{1-6}alkoxy;

or when R^2 is adjacent to R^1, they may be joined together such that there is formed a 5- or 6-membered saturated or unsaturated ring containing one or two atoms selected from nitrogen, oxygen and sulphur, which ring is optionally substituted by a group selected from C_{1-4}alkyl, CF_3, =O or =S;

R^3 represents hydrogen, halogen, C_{1-6}alkyl, fluoroC_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkoxy, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, cyano, SR^a, SOR^a, SO_2R^a, NR^aR^b, NR^aCOR^{14}, COR^a, CO_2R^a, $CONR^aR^b$ or C_{1-4}alkyl substituted by cyano, CO_2R^a or $CONR^aR^b$ where R^a and R^b are as previously defined;

or R^3 represents a 5- or 6-membered aromatic heterocyclic group containing 1, 2, 3 or 4 heteroatoms, selected from nitrogen, oxygen and sulphur,

which group is optionally substituted by one or two groups selected from C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, trifluoromethyl, OCF_3, NO_2, CN, SR^a, SOR^a, SO_2R^a, COR^a, CO_2R^a, phenyl, $-(CH_2)_rNR^aR^b$, $-(CH_2)_rNR^aCOR^b$, $-(CH_2)_rCONR^aR^b$, or $CH_2C(O)R^a$, where R^a and R^b are as previously defined and r is zero, 1 or 2;

R^4 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy, hydroxy, NO_2, CN, SR^a, SOR^a, SO_2R^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl substituted by C_{1-4}alkoxy, wherein R^a and R^b are as previously defined;

R^5 is hydrogen, halogen, C_{1-6}alkyl, fluoroC_{1-6}alkyl or C_{1-6}alkoxy substituted by C_{1-4}alkoxy;

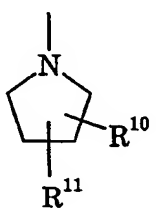
R^6 represents hydrogen, hydroxy or a C_{1-4}alkyl group optionally substituted by a hydroxy group;

R^7 represents hydrogen, hydroxy, $-(CH_2)_nNR^8R^9$, $-(CH_2)_nCO_2R^a$, carbocyclyl, C-linked heterocyclyl or heteroaryl;

or R^6 and R^7 together represent =O, $=CHCO_2R^a$ or $-O(CH_2)_mO-$;

R^8 and R^9 each independently represent hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, hydroxyC_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl, $(CH_2)_q$heterocyclyl, CHO, $C(O)C_{1-6}$alkyl, $C(O)(CH_2)_qC_{3-7}$cycloalkyl, $C(O)(CH_2)_q$aryl, $C(O)(CH_2)_q$heterocyclyl, $C(O)(CH_2)_pNR^aR^b$, $(CH_2)_qCO_2C_{1-6}$alkyl, $CO_2(CH_2)_qC_{3-7}$cycloalkyl, $CO_2(CH_2)_q$aryl, $CO_2(CH_2)_q$heterocyclyl, $CO_2(CH_2)_pNR^aR^b$, $(CH_2)_pNR^aCOR^b$, $(CH_2)_pNR^aCO_2R^b$, $(CH_2)_qCONR^a$aryl or $(CH_2)_qCONR^a$heterocyclyl where R^a and R^b are as previously defined;

or R^8 and R^9, together with the nitrogen atom to which they are attached, represent a heteroaliphatic ring selected from the group consisting of:



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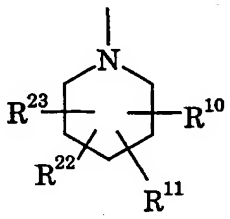

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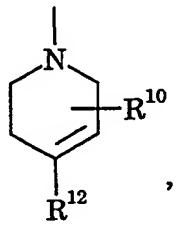

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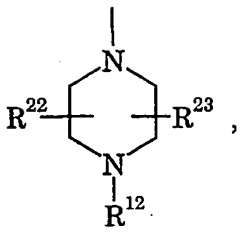
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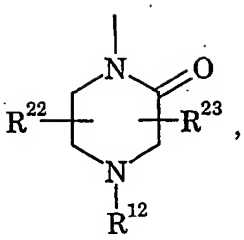
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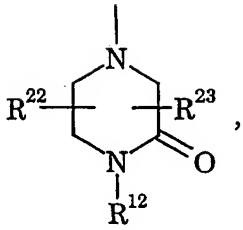
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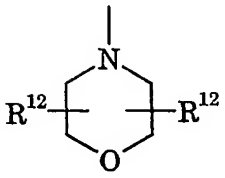
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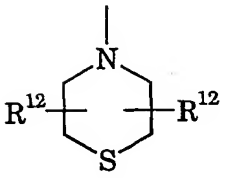
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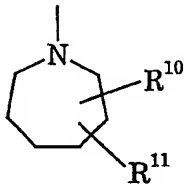
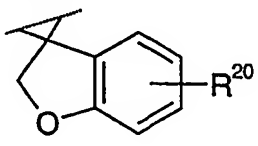

;

R^{10} and R^{11} each independently represent hydrogen, halogen, hydroxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, hydroxyC_{1-6}alkyl, fluoroC_{1-6}alkyl, C_{1-6}alkoxy, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl, (C_{2-6}alkenyl)aryl, (C_{2-6}alkynyl)aryl, $(CH_2)_q$heterocyclyl, $(CH_2)_qNR^aR^b$, $O(CH_2)_qC_{3-7}$cycloalkyl, $O(CH_2)_q$aryl, $O(CH_2)_q$heterocyclyl, $O(CH_2)_pNR^aR^b$, $OC(O)C_{1-6}$alkyl, $C(O)C_{1-6}$alkyl, $C(O)(CH_2)_q$aryl, $C(O)(CH_2)_q$heterocyclyl, $C(O)(CH_2)_qNR^aR^b$, CO_2H, CO_2C_{1-6}alkyl, $CO_2(CH_2)_qC_{3-7}$cycloalkyl, $CO_2(CH_2)_q$aryl, $CO_2(CH_2)_q$heterocyclyl or $CO_2(CH_2)_pNR^aR^b$, where R^a and R^b are as previously defined;

or, when they are attached to the same carbon atom, R^{10} and R^{11} may together represent =O, $=CHCO_2R^a$, $-O(CH_2)_mO-$, $-CH_2O(CH_2)_s-$, $-CH_2OCH_2C(O)-$, $-CH_2OCH_2CH(OH)-$, $-CH_2OCH_2C(CH_3)_2-$, $-CH_2OC(CH_3)_2CH_2-$, $-C(CH_3)_2OCH_2CH_2-$, $-CH_2C(O)OCH_2-$, $-OC(O)CH_2CH_2-$, $-C(O)OCH_2CH_2-$, $-C(O)OC(CH_3)_2CH_2-$, $-C(O)OCH_2C(CH_3)_2-$, $-OCH_2(CH_2)_s-$, $-OC(CH_3)_2CH_2CH_2-$, $-OCH_2C(CH_3)_2CH_2-$, $-OCH_2CH_2C(CH_3)_2-$, $-OCH_2CH=CHCH_2-$, $-OCH_2CH(OH)CH_2CH_2-$, $-OCH_2CH_2CH(OH)CH_2-$, $-OCH_2C(O)CH_2CH_2-$, $-OCH_2CH_2C(O)CH_2-$, or a group of the formula


;

or, where they are attached to adjacent carbon atoms, R^{10} and R^{11} may together represent $-OCH_2CH_2-$ or $-OCH_2CH(OH)-$, or R^{10} and R^{11} may together form a fused benzene ring;

or, R^{10} and R^{11} together form a C_{1-2}alkylene bridge across the pyrrolidine, piperidine or hexamethyleneimine ring to which they are attached;

R^{12} represents hydrogen, C_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl, $(CH_2)_q$heterocyclyl, CHO, $C(O)C_{1-6}$alkyl, $C(O)(CH_2)_qC_{3-7}$cycloalkyl, $C(O)(CH_2)_q$aryl, $C(O)(CH_2)_q$heterocyclyl, CO_2C_{1-6}alkyl, $CO_2(CH_2)_qC_{3-7}$cycloalkyl, $CO_2(CH_2)_q$aryl, $CO_2(CH_2)_q$heterocyclyl or $CO_2(CH_2)_pNR^aR^b$, where R^a and R^b are as previously defined;

or, where they are attached to adjacent carbon atoms, R^{12} and R^{18} may together form a fused imidazolyl or triazolyl ring;

R^{13} represents hydrogen, C_{1-6}alkyl or $C(O)C_{1-6}$alkyl;

R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} each independently represent hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkenyl, hydroxyC_{1-6}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, $(CH_2)_pNR^aR^b$, CHO, $C(O)C_{1-6}$alkyl or CO_2C_{1-6}alkyl;

or, R^{14} and R^{15} together represent $-CH_2CH_2-$;

or, R^{16} and R^{17} together represent $-CH_2CH_2-$;

or, R^{18} and R^{19} together represent $-CH_2CH_2-$;

R^{20} represents hydrogen, halogen, hydroxy, C_{1-4}alkyl, hydroxyC_{1-4}alkyl or fluoroC_{1-4}alkyl;

R^{21a} represents hydrogen, halogen or hydroxy and R^{21b} represents hydrogen;

or R^{21a} and R^{21b} both represent fluorine or together represent oxo (=O);

R^{22} and R^{23} each independently represent hydrogen, halogen, hydroxy, C_{1-6}alkyl or oxo (=O);

n is zero, 1 or 2;

m is 1 or 2;

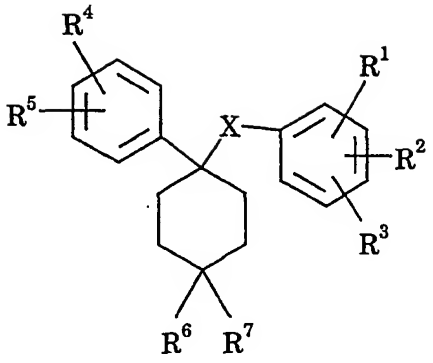
p is 1, 2, 3 or 4;

q is zero, 1, 2, 3 or 4; and

s is 1, 2 or 3;

and pharmaceutically acceptable salts and N-oxides thereof.

According to an alternative embodiment, the present invention also provides compounds of the formula (I'):



(I')

wherein

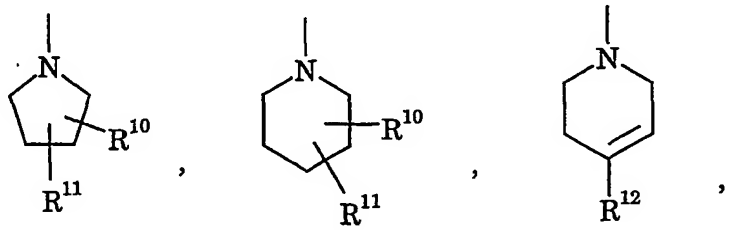
R^6 represents hydrogen or a C_{1-4}alkyl group optionally substituted by a hydroxy group;

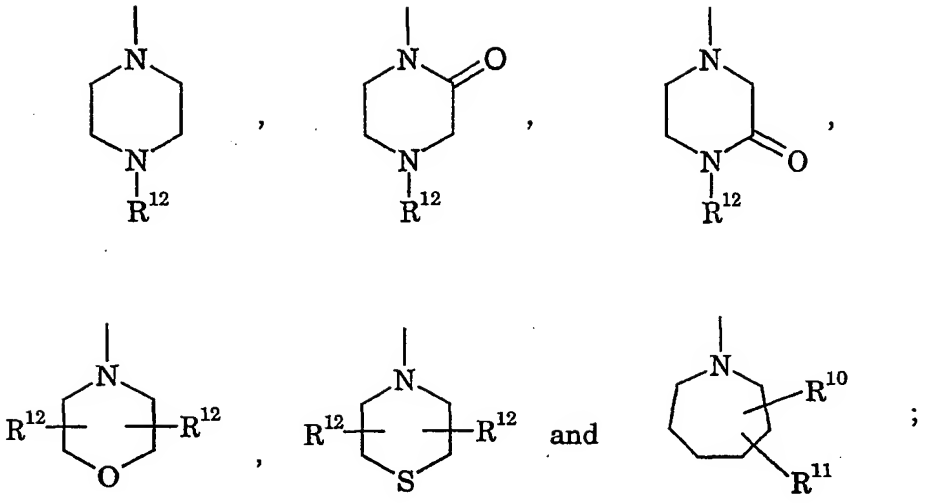
R^7 represents hydrogen, hydroxy, $-(CH_2)_nNR^8R^9$, $-(CH_2)_nCO_2R^a$, carbocyclyl or heteroaryl;

or R^6 and R^7 together represent =O, $=CHCO_2R^a$ or $-O(CH_2)_mO-$;

R^8 and R^9 each independently represent hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl, $(CH_2)_q$heterocyclyl, CHO, $C(O)C_{1-6}$alkyl, $C(O)(CH_2)_qC_{3-7}$cycloalkyl, $C(O)(CH_2)_q$aryl, $C(O)(CH_2)_q$heterocyclyl, $C(O)(CH_2)_pNR^aR^b$, $(CH_2)_qCO_2C_{1-6}$alkyl, $CO_2(CH_2)_qC_{3-7}$cycloalkyl, $CO_2(CH_2)_q$aryl, $CO_2(CH_2)_q$heterocyclyl, $CO_2(CH_2)_pNR^aR^b$, $(CH_2)_pNR^aCOR^b$ or $(CH_2)_pNR^aCO_2R^b$, where R^a and R^b are as previously defined;

or R^8 and R^9, together with the nitrogen atom to which they are attached, represent a heteroaliphatic ring selected from the group consisting of:





R^{10} and R^{11} each independently represent hydrogen, halogen, hydroxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, hydroxyC_{1-6}alkyl, C_{1-6}alkoxy, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl, (C_{2-6}alkenyl)aryl, (C_{2-6}alkynyl)aryl, $(CH_2)_q$heterocyclyl, $(CH_2)_qNR^aR^b$, $O(CH_2)_qC_{3-7}$cycloalkyl, $O(CH_2)_q$aryl, $O(CH_2)_q$heterocyclyl, $O(CH_2)_pNR^aR^b$, $OC(O)C_{1-6}$alkyl, $C(O)C_{1-6}$alkyl, $C(O)(CH_2)_q$aryl, $C(O)(CH_2)_q$heterocyclyl, $C(O)(CH_2)_qNR^aR^b$, CO_2H, CO_2C_{1-6}alkyl, $CO_2(CH_2)_qC_{3-7}$cycloalkyl, $CO_2(CH_2)_q$aryl, $CO_2(CH_2)_q$heterocyclyl or $CO_2(CH_2)_pNR^aR^b$, where R^a and R^b are as previously defined;

or, when they are attached to the same carbon atom, R^{10} and R^{11} together represent =O, $=CHCO_2R^a$, $-O(CH_2)_mO-$, $-OCH_2CH_2CH_2-$, $-CH_2OCH_2CH_2-$ or $-CH_2OCH_2C(O)-$;

or, where they are attached to adjacent carbon atoms, R^{10} and R^{11} together form a fused benzene ring;

or, R^{10} and R^{11} together form a C_{1-2}alkylene bridge across the pyrrolidine, piperidine or hexamethyleneimine ring to which they are attached;

R^{12} represents hydrogen, C_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl, $(CH_2)_q$heterocyclyl, CHO, $C(O)C_{1-6}$alkyl, $C(O)(CH_2)_qC_{3-7}$cycloalkyl, $C(O)(CH_2)_q$aryl, $C(O)(CH_2)_q$heterocyclyl, CO_2C_{1-6}alkyl, $CO_2(CH_2)_qC_{3-7}$cycloalkyl, $CO_2(CH_2)_q$aryl, $CO_2(CH_2)_q$heterocyclyl or $CO_2(CH_2)_pNR^aR^b$, where R^a and R^b are as previously defined;

R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} each independently represent hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkenyl, hydroxyC_{1-6}alkyl, $(CH_2)_pNR^aR^b$, CHO, $C(O)C_{1-6}$alkyl or CO_2C_{1-6}alkyl;

and X, R^1, R^2, R^3, R^4, R^5, R^{13}, n, m, p and q are as defined in relation to formula (I);

and pharmaceutically acceptable salts thereof.

A preferred class of compound of formula (I) is that wherein R^1 is hydroxy, C_{1-6}alkyl, fluoroC_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, fluoroC_{1-6}alkoxy, C_{2-6}alkenyloxy, C_{3-7}cycloalkoxy, C_{3-7}cycloalkylC_{1-4}alkoxy, cyano, NR^aR^b, SR^a, OSO_2R^a, or R^1 together with the group R^2 form a 5-membered saturated ring containing one oxygen atom.

A particularly preferred class of compound of formula (I) is that wherein R^1 is C_{1-6}alkyl, fluoroC_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkoxy, C_{3-7}cycloalkoxy or C_{3-7}cycloalkoxyC_{1-4}alkyl, especially methyl, trifluoromethyl, methoxy, trifluoromethoxy, 2,2,2-trifluoroethoxy, difluoromethoxy, cyclopropoxy or cyclopropylmethoxy.

Another preferred class of compound of formula (I) is that wherein R^2 is a hydrogen, fluorine or chlorine atom, especially a hydrogen atom.

A further preferred class of compound of formula (I) is that wherein R^3 is hydrogen, halogen, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy, cyano, NR^aR^b, NR^aCOR^d (where R^d is methyl, methoxy, trifluoromethyl or phenyl), or a 5-membered aromatic heterocyclic group as previously defined.

Also preferred is the class of compound of formula (I) in which R^3 is C_{1-6}alkyl, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy or a 5-membered aromatic heterocyclic group as previously defined, especially methyl, trifluoromethyl, trifluoromethoxy or 5-trifluoromethyl-1,2,3,4-tetrazol-1-yl.

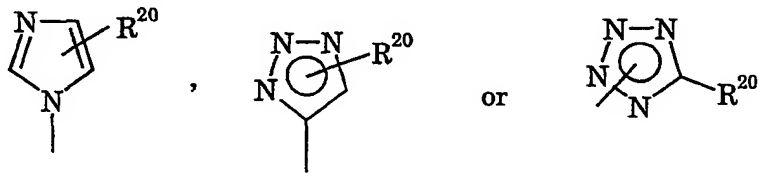
Certain particularly apt compounds of the present invention include those wherein R^3 is a group selected from pyrrole, furan, thiene, pyridine, pyrazole, imidazole, oxazole, isoxazole, thiazole, isothiazole, pyrazine, pyrimidine, pyridazine, triazole, oxadiazole, thiadiazole, triazine, and tetrazole, each heteroaryl group being optionally substituted as previ usly defined.

Preferred compounds of the present invention are thos wherein R^3 is a group selected from furan, pyridine, pyrazole, imidazole, oxazole, isoxazole,

pyrazine, pyrimidine, thiazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole and tetrazole, each heteroaryl group being optionally substituted as previously defined.

Particularly preferred compounds of the present invention are those wherein R^3 is a group selected from furan, pyridine, pyrimidine, 1,2,3-triazole, 1,2,4-triazole and tetrazole, each heteroaryl group being optionally substituted as previously defined.

An especially preferred class of compound of formula (I) is that wherein R^3 is the group



where R^{20} is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, CF_3, OCF_3, NO_2, CN, SR^a, SOR^a, SO_2R^a, COR^a, CO_2R^a, $(CH_2)_rCONR^aR^b$, $(CH_2)_rNR^aR^b$ or $(CH_2)_rNR^aCOR^b$, where R^a, R^b and r are as previously defined.

R^{20} is preferably hydrogen, C_{1-4}alkyl, especially methyl, CF_3, $(CH_2)_rCONR^aR^b$, SOR^a or SO_2R^a where R^a and R^b are preferably hydrogen, C_{1-4}alkyl or fluoroC_{1-4}alkyl and r is as previously defined. Most especially, R^{20} is CF_3.

Preferably R^1 and R^3 are in the 3 and 5 positions of the phenyl ring.

More preferably R^1 is 3-fluoro or 3-CF_3.

More preferably R^3 is 5-fluoro or 5-CF_3.

More preferably R^2 is hydrogen.

Most preferably R^1 is 3-CF_3, R^2 is hydrogen and R^3 is 5-CF_3.

Another preferred class of compounds of formula (I) is that wherein R^1 and R^3 are in the 2- and 5-positions of the phenyl ring.

In this sub-class of compounds of formula (I), R^1 is preferably C_{1-6}alkoxy or C_{3-7}cycloalkoxy, especially methoxy or cyclopropoxy.

Also in this sub-class of compounds of formula (I), R^2 is preferably hydrogen.

Also, in this sub-class of compounds of formula (I) R^3 is preferably hydrogen, C_{1-6}alkoxy, fluoroC_{1-6}alkoxy or a 5-membered aromatic heterocyclic group as previously defined. Most especially, R^3 is hydrogen, methoxy or trifluoromethoxy.

A further preferred class of compound of formula (I) is that wherein R^4 is hydrogen.

Another preferred class of compounds of formula (I) is that wherein R^5 is hydrogen, fluorine, chlorine or CF_3, especially hydrogen or fluorine.

Preferably R^4 is hydrogen and R^5 is hydrogen or 4-fluoro.

Another further preferred class of compounds of formula (I) is that wherein R^6 is hydrogen.

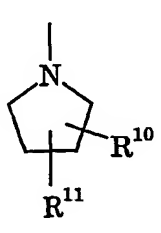
A further preferred class of compounds of formula (I) is that wherein R^7 is hydroxy, $-(CH_2)_nNR^8R^9$, a C-linked heterocyclyl group or R^6 and R^7 together represent =O, $-O(CH_2)_mO-$ or $-CH_2OCH_2C(O)-$.

Another preferred class of compounds of formula (I) is that wherein R^7 is hydroxy or $-(CH_2)_nNR^8R^9$, or R^6 and R^7 together represent =O, $-O(CH_2)_mO-$ or $-CH_2OCH_2C(O)-$.

A further preferred class of compounds of formula (I) is that wherein R^8 represents hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, hydroxyC_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl, $(CH_2)_q$heterocyclyl, $C(O)C_{1-6}$alkyl, $C(O)(CH_2)_q$aryl, $C(O)(CH_2)_q$heterocyclyl, $C(O)(CH_2)_pNR^aR^b$, $(CH_2)_qCO_2C_{1-6}$alkyl, $(CH_2)_pNR^aCO_2R^b$ or $(CH_2)_qCONR^a$aryl;

and R^9 represents hydrogen, C_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl or CO_2C_{1-6}alkyl;

or R^8 and R^9 together with the nitrogen atom to which they are attached represent a heteroaliphatic ring selected from the group consisting of



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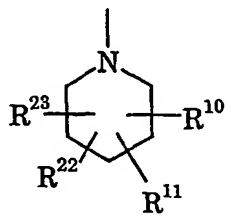

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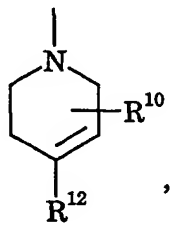

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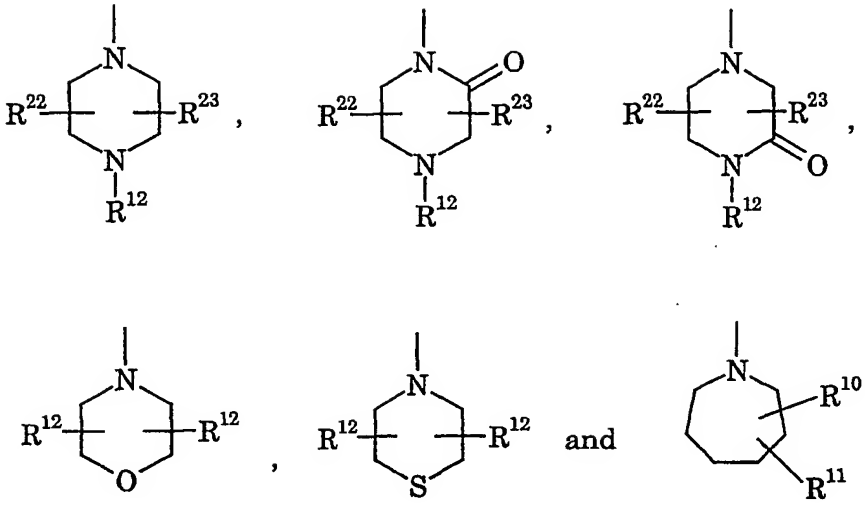
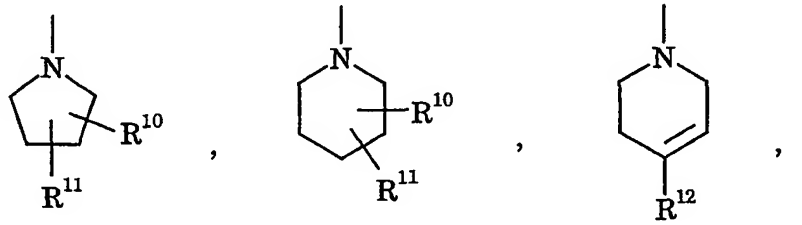
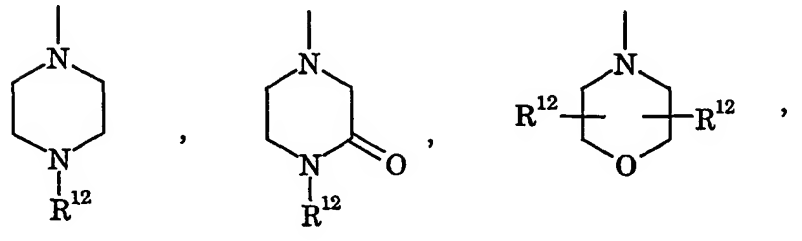


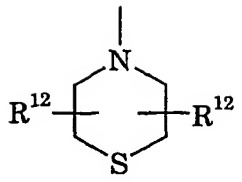
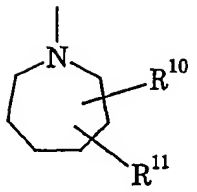
A yet further preferred class of compounds of formula (I) is that wherein R^8 represents hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl, $(CH_2)_q$heterocyclyl, $C(O)C_{1-6}$alkyl, $C(O)(CH_2)_q$aryl, $C(O)(CH_2)_q$heterocyclyl, $C(O)(CH_2)_pNR^aR^b$, $(CH_2)_qCO_2C_{1-6}$alkyl or $(CH_2)_pNR^aCO_2R^b$;

and R^9 represents hydrogen, C_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl or CO_2C_{1-6}alkyl;

or R^8 and R^9 together with the nitrogen atom to which they are attached represent a heteroaliphatic ring selected from the group consisting of



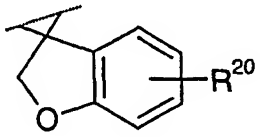


A further preferred class of compounds of formula (I) is that wherein R^{10} represents hydrogen, hydroxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, hydroxyC_{1-6}alkyl, fluoroC_{1-6}alkyl, (C_{2-6}alkynyl)aryl, $(CH_2)_q$aryl, $(CH_2)_q$heterocyclyl, $(CH_2)_qNR^aR^b$, $OC(O)C_{1-6}$alkyl, $C(O)(CH_2)_qNR^aR^b$, CO_2H or CO_2C_{1-6}alkyl;

and R^{11} represents hydrogen, halogen, hydroxy, C_{1-6}alkyl or $(CH_2)_q NR^aR^b$;

or when they are attached to the same carbon atom, R^{10} and R^{11} may together represent =O, $-O(CH_2)_mO-$, $-CH_2O(CH_2)_s-$, $-CH_2OCH_2C(O)-$, $-CH_2OCH_2CH(OH)-$, $-CH_2OCH_2C(CH_3)_2-$, $-CH_2OC(CH_3)_2CH_2-$, $-C(CH_3)_2OCH_2CH_2-$, $-CH_2C(O)OCH_2-$, $-OC(O)CH_2CH_2-$, $-C(O)OCH_2CH_2-$, $-C(O)OC(CH_3)_2CH_2-$, $-C(O)OCH_2C(CH_3)_2-$, $-OCH_2(CH_2)_s-$, $-OC(CH_3)_2CH_2CH_2-$, $-OCH_2CH=CHCH_2-$, $-OCH_2CH(OH)CH_2CH_2-$, $-OCH_2CH_2CH(OH)CH_2-$, $-OCH_2C(O)CH_2CH_2-$, or a group of the formula



;

or, when they are attached to adjacent carbon atoms, R^{10} and R^{11} may together represent $-OCH_2CH_2-$ or $-OCH_2CH(OH)-$, or R^{10} and R^{11} may together form a fused benzene ring;

or R^{10} and R^{11} together form a C_{1-2}alkylene bridge across the pyrrolidine or piperidine ring to which they are attached.

Another preferred class of compounds of formula (I) is that wherein R^{10} represents hydrogen, hydroxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, hydroxyC_{1-6}alkyl, (C_{2-6}alkynyl)aryl, $(CH_2)_q$aryl, $(CH_2)_q$heterocyclyl, $(CH_2)_qNR^aR^b$, $OC(O)C_{1-6}$alkyl, $C(O)(CH_2)_qNR^aR^b$, CO_2H or CO_2C_{1-6}alkyl;

and R^{11} represents hydrogen, halogen, hydroxy, C_{1-6}alkyl or $(CH_2)_q NR^aR^b$;

or when they are attached to the same carbon atom, R^{10} and R^{11} together represent =O or $-O(CH_2)_mO-$;

or, when they are attached to adjacent carbon atoms, R^{10} and R^{11} together form a fused benzene ring;

or R^{10} and R^{11} together form a C_{1-2}alkylene bridge across the pyrrolidine or piperidine ring to which they are attached.

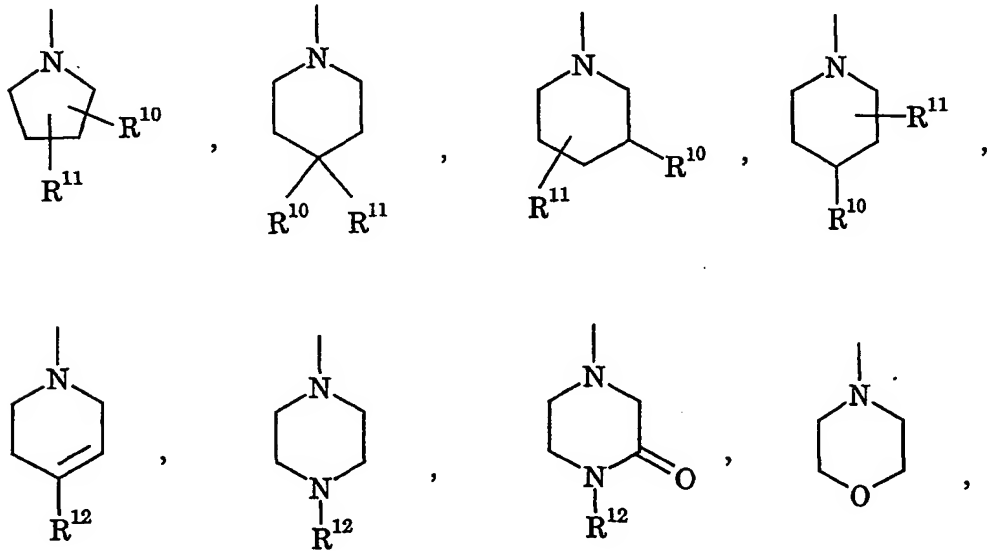
A further preferred class of compounds of formula (I) is that wherein R^{12} represents hydrogen, C_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl, $(CH_2)_q$heterocyclyl, CHO, $C(O)C_{1-6}$alkyl, $C(O)C_{3-7}$cycloalkyl, $C(O)(CH_2)_q$aryl or CO_2C_{1-6}alkyl.

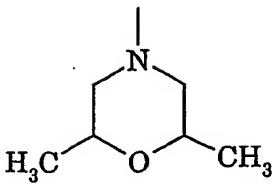
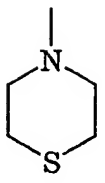
A yet further prefered class of compounds of formula (I) is that wherein R^9 represents hydrogen, C_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl or CO_2C_{1-6}alkyl.

A particularly preferred class of compounds of formula (I) is that wherein R^8 represents hydrogen, C_{1-6}alkyl, C_{2-4}alkenyl, C_{3-7}cycloalkyl, CH_2C_{3-7}cycloalkyl, $(CH_2)_q$phenyl, $(CH_2)_q$furyl, $(CH_2)_q$pyridyl, $(CH_2)_q$triazolinone, $C(O)C_{1-4}$alkyl, $C(O)(CH_2)_q$phenyl, $C(O)(CH_2)_q$imidazolyl, $C(O)(CH_2)_q$tetrazolyl, $C(O)(CH_2)$pyrrolidinyl, $C(O)(CH_2)_pNR^aR^b$, $CH_2C(O)C_{1-4}$alkyl or $(CH_2)_pNR^aCO_2C_{1-4}$alkyl;

and R^9 represents hydrogen, C_{1-6}alkyl, CH_2C_{3-5}cycloalkyl or CO_2C_{1-4}alkyl;

or R^8 and R^9 together with the nitrogen atom to which they are attached represent a heteroaliphatic ring selected from the group consisting of:

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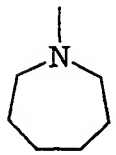


A further particularly preferred class of compounds of formula (I) is that wherein:

R^{10} represents hydrogen, hydroxy, methyl, allyl, acetylene, hydroxyC_{1-4}alkyl, -C≡C(phenyl), phenyl, 4-fluorophenyl, CH_2phenyl, CH_2CH_2phenyl, heterocyclyl (wherein said heterocyclyl is selected from the group consisting of pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, and hexamethyleneimine, wherein each ring is optionally substituted by one or two groups selected from methyl, hydroxymethyl, cyclohexyl, dimethylamino and benzisothiazole or there is optionally a benzene ring fused to the ring, or there is optionally present a $-CH_2CH_2-$ bridge across the ring), NR^aR^b, $OC(O)CH_3$, $C(O)NR^aR^b$, CO_2H or CO_2C_{1-4}alkyl; and

R^{11} represents hydrogen, fluorine, hydroxy, methyl or dimethylamino;

or, when they are attached to the same carbon atom, R^{10} and R^{11} together represent =O or $-OCH_2CH_2O-$;

or, when they are attached to adjacent carbon atoms, R^{10} and R^{11} together form a fused benzene ring;

or, R^{10} and R^{11} together form a $-CH_2CH_2-$ bridge across the pyrrolidine or piperidine ring to which they are attached.

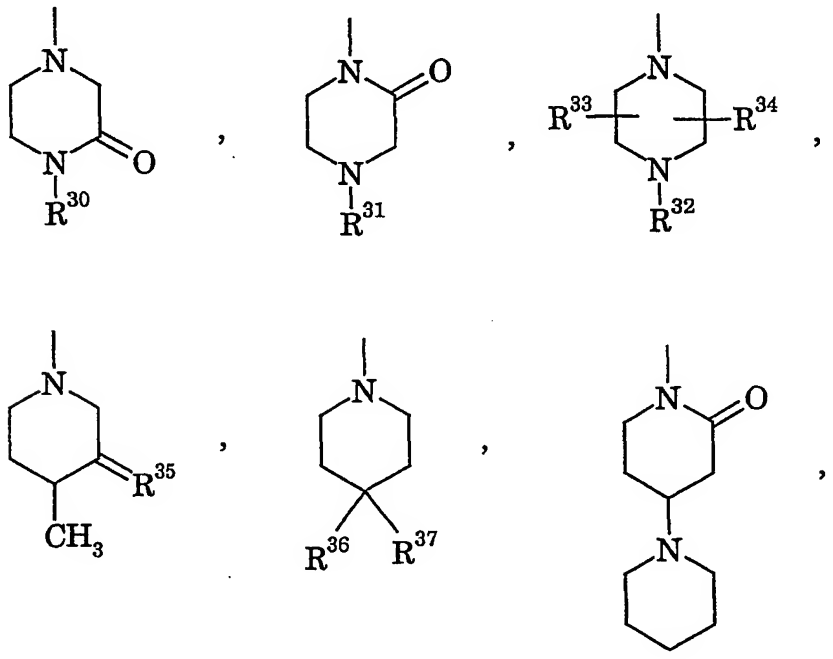
A yet further particularly preferred class of compounds of formula (I) is that wherein R^{12} represents hydrogen, C_{1-6}alkyl, C_{3-6}cycloalkyl, CH_2C_{3-6}cycloalkyl (especially CH_2cyclopropyl or CH_2cyclohexyl), phenyl, CH_2phenyl, CH_2CH_2phenyl (wherein each of said phenyl groups are optionally substituted by one or two substituents selected from fluorine, CF_3 or methoxy), CH_2heterocyclyl (wherein said heterocyclyl is selected from the group consisting of 2-, 3- or 4-pyridine, 2- or 3-thiophene, 2- or 3-furan, thiazole, and benzisothiazole), CHO, $C(O)C_{1-4}$alkyl, $C(O)C_{3-6}$cycloalkyl (especially C(O)cyclopropyl or C(O)cyclohexyl), $C(O)CH_2$cycloalkyl (especially $C(O)CH_2$cyclopropyl or $C(O)CH_2$cyclohexyl),

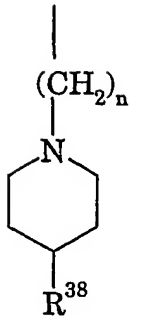
$C(O)CH_2CH_2C_{3-6}$cycloalkyl (especially $C(O)CH_2CH_2$cyclohexyl), C(O)phenyl or CO_2C_{1-4}alkyl.

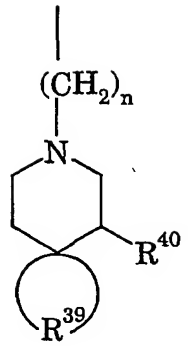
Yet another particularly preferred class of compounds of formula (I) is that wherein R^9 represents hydrogen, C_{1-6}alkyl, CH_2C_{3-5}cycloalkyl or CO_2C_{1-4}alkyl.

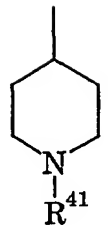
Another preferred class of compound of formula (I) is that wherein the ring A is a phenyl ring.

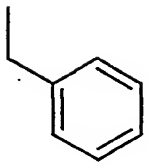
Particularly preferred compounds of formula (I) are those wherein R^7 represents a group selected from:





,


,


, and

,

wherein

R^{30} represents 4-pyridyl, phenyl, phenyl mono-substituted by fluorine, chlorine, methyl, methoxy or CO_2methoxy, or phenyl disubstituted by methyl;

R^{31} represents C_{2-4}alkyl or $(CH_2)_qC_{3-7}$cycloalkyl, especially *tert*-butyl, cyclopropylmethyl or cyclohexyl;

R^{32} represents C_{1-6}alkyl, tetrahydropyranyl or benzyl;

R^{33} and R^{34}, which may be attached to the same or different carbon atoms, each independently represent hydrogen or methyl;

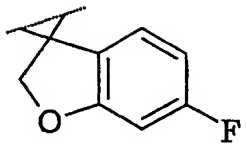
R^{35} represents hydroxy or methoxy;

R^{36} represents hydroxyC_{1-4}alkyl (especially hydroxymethyl), C_{1-4}alkoxy (especially methoxy) or hydroxy;

R^{37} represents methoxy C_{2-4}alkyl (especially methoxymethyl) or C_{2-4}alkyl;

R^{38} represents hydrogen, oxo (=O), hydroxy, trifluoromethyl, C_{1-3}alkyl (especially isopropyl) or hydroxyC_{1-3}alkyl (especially hydroxymethyl or hydroxyethyl);

R^{39} represents a ring-forming moiety selected from $-OCH_2CH_2O-$, $-CH_2OCH_2CH_2-$, $-CH_2OCH_2CH_2CH_2-$, $-CH_2OCH_2C(O)-$, $-CH_2OCH_2CH(OH)-$, $-CH_2OC(CH_3)_2CH_2-$, $-C(CH_3)_2OCH_2CH_2-$, $-CH_2C(O)OCH_2-$, $-C(O)OCH_2CH_2-$, $-C(O)OC(CH_3)_2CH_2-$, $-OCH_2CH_2CH_2-$, $-OCH_2CH_2CH_2CH_2-$, $-OC(CH_3)_2CH_2CH_2$, $-OCH_2CH=CHCH_2-$, $-OCH_2CH(OH)CH_2CH_2-$, $-OCH_2CH_2CH(OH)CH_2-$, $-OCH_2C(O)CH_2CH_2-$ and a group of the formula



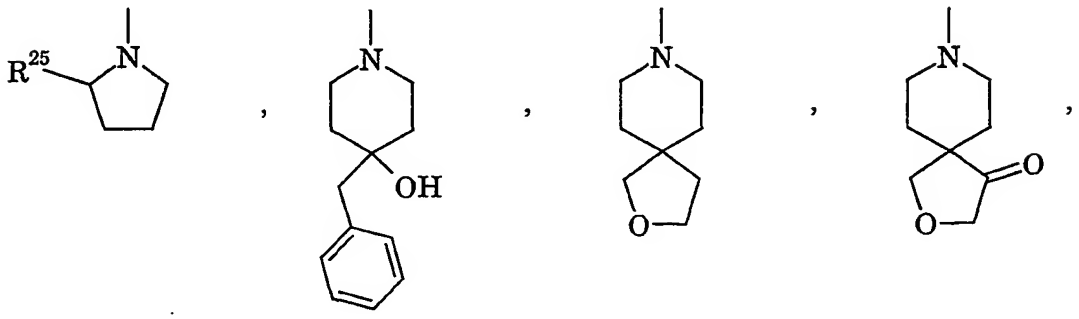
;

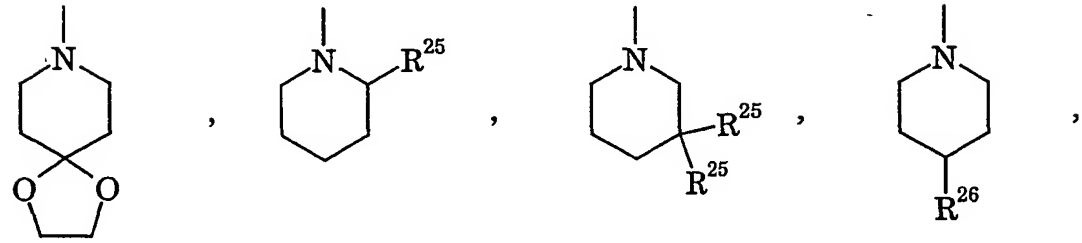
R^{40} is hydrogen or hydroxy, especially hydrogen;

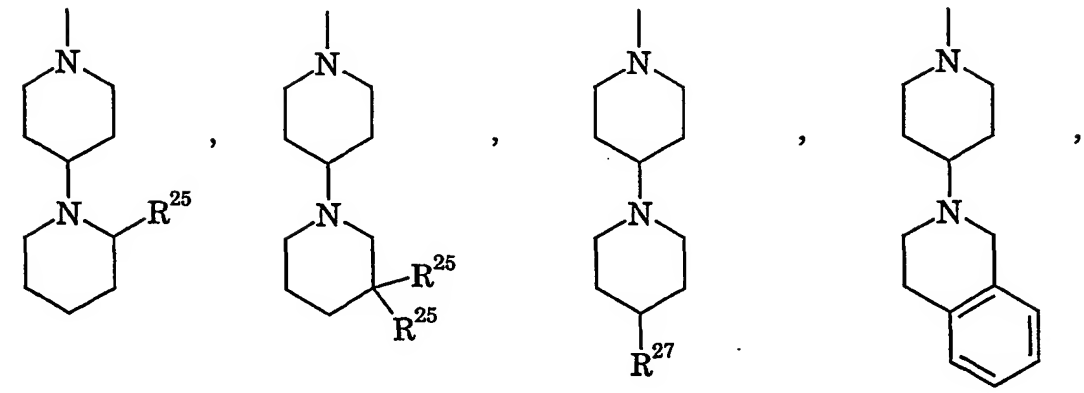
R^{41} is C_{1-3}alkyl, especially isopropyl; and

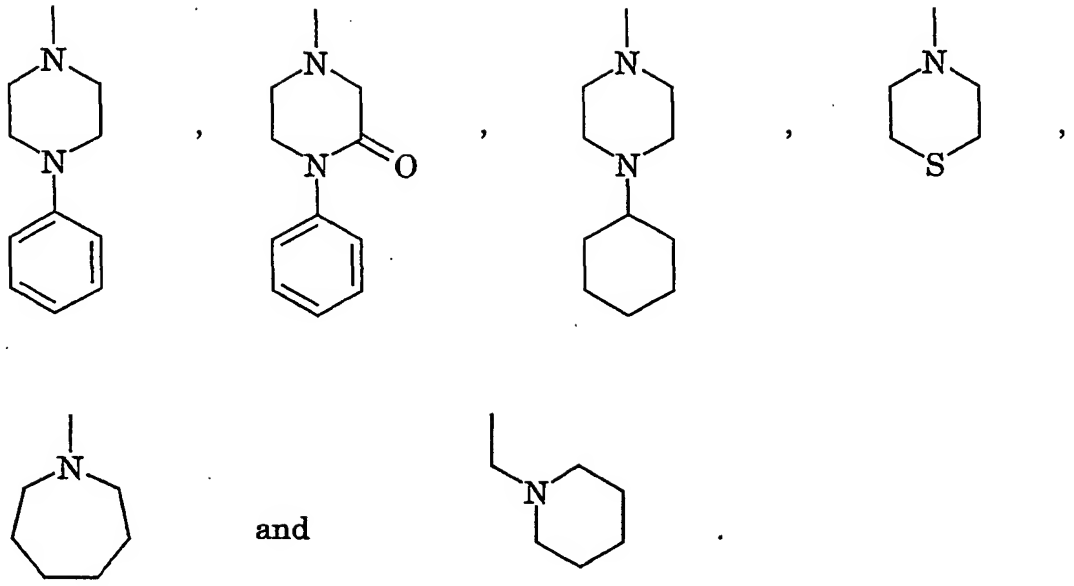
n is zero, 1 or 2, especially zero.

Further preferred compounds of formula (I) are those wherein R^7 represents a group selected from:









wherein

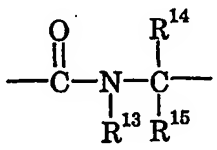
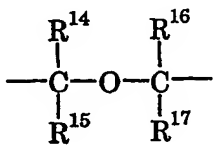
R^{25} represents hydrogen, methyl or hydroxymethyl;

R^{26} represents hydrogen, methyl, hydroxy, methylamino, dimethylamino, cyclopropylamino, phenyl, or phenyl substituted by fluorine; and

R^{27} represents hydrogen, methyl, hydroxy, methylamino, dimethylamino or cyclopropylamino.

Another preferred class of compounds of formula (I) is that wherein R^{21a} represents hydrogen, fluorine or hydroxy and R^{21b} is hydrogen, or R^{21a} and R^{21b} both represent fluorine or together represent oxo (=O). In particular, R^{21a} is preferably hydrogen, fluorine or hydroxy and R^{21b} is hydrogen. Most especially, R^{21a} and R^{21b} are preferably both hydrogen.

Another preferred class of compounds of formula (I) is that wherein X represents a linker selected from:

(a)  , and (b)  .

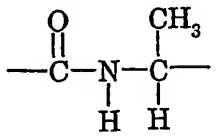
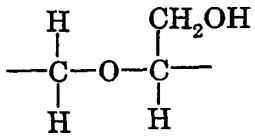
Another preferred class of compounds of formula (I) is that wherein R^{13} represents hydrogen, methyl or acetyl. In particular, R^{13} represents hydrogen.

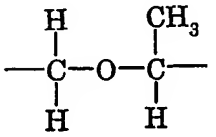
A further preferred class of compounds of formula (I) is that wherein one of the groups R^{14}, R^{15}, R^{16} and R^{17} represents hydrogen, hydroxy, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, $(CH_2)_pNR^aR^b$, CHO, $C(O)C_{1-6}$alkyl or CO_2C_{1-6}alkyl, and the other(s) of the groups R^{14}, R^{15}, R^{16} and R^{17} each represent hydrogen.

A particularly preferred class of compounds of formula (I) is that wherein one of the groups R^{14}, R^{15}, R^{16} and R^{17} represents methyl or hydroxymethyl, and the other(s) of groups R^{14}, R^{15}, R^{16} and R^{17} each represent hydrogen.

A further preferred class of compounds of formula (I) is that wherein R^{18} and R^{19} each independently represent hydrogen or methyl.

Most especially, a preferred class of compounds of formula (I) is that wherein X represents a linker selected from:

(a)  , (b)  , and

(c)  .

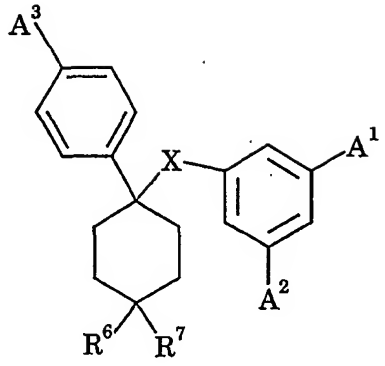
Another preferred class of compounds of formula (I) is that wherein n is zero.

A further preferred class of compounds of formula (I) is that wherein m is 2.

Another preferred class of compounds of formula (I) is that wherein p is 1, 2 or 3, particularly 1 or 2, and especially 1.

A further preferred class of compounds of formula (I) is that wherein q is zero, 1 or 2, particularly zero or 1.

One favoured group of compounds of the present invention are of the formula (Ia) and pharmaceutically acceptable salts thereof:



(Ia)

wherein

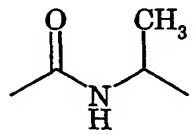
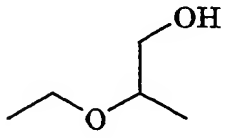
A^1 is fluorine or CF_3;

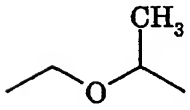
A^2 is fluorine or CF_3;

A^3 is fluorine or hydrogen;

R^6 and R^7 are as defined in relation to formula (I); and

X is a linker selected from:

(a)  , (b)  , and

(c)  .

When any variable occurs more than one time in formula (I) or formula (Ia) or in any substituent, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "alkyl" or "alkoxy" as a group or part of a group means that the group is straight or branched. Examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-but xy.

As used herein, the term "hydroxyC_{1-6}alkyl" means a C_{1-6}alkyl group in which one or more (in particular 1 to 3, and especially 1) hydrogen atoms have

been replaced by hydroxy groups. Particularly preferred are hydroxyC_{1-3}alkyl groups, for example, CH_2OH, CH_2CH_2OH, $CH(CH_3)OH$ or $C(CH_3)_2OH$, and most especially CH_2OH.

As used herein, the terms "fluoroC_{1-6}alkyl" and fluoroC_{1-6}alkoxy" means a C_{1-6}alkyl or C_{1-6}alkoxy group in which one or more (in particular, 1 to 3) hydrogen atoms have been replaced by fluorine atoms. Particularly preferred are fluoroC_{1-3}alkyl and fluoroC_{1-3}alkoxy groups, for example, CF_3, CH_2CH_2F, CH_2CHF_2, CH_2CF_3, OCF_3, OCH_2CH_2F, OCH_2CHF_2 or OCH_2CF_3, and most especially CF_3, OCF_3 and OCH_2CF_3.

The cycloalkyl groups referred to herein may represent, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. A suitable $(CH_2)_qC_{3-7}$cycloalkyl group where q is 1 may be, for example, cyclopropylmethyl or cyclohexylmethyl.

Similarly cycloalkoxy groups referred to herein may represent, for example, cyclopropoxy or cyclobutoxy.

As used herein, the terms "alkenyl" and "alkynyl" as a group or part of a group means that the group is straight or branched. Examples of suitable alkenyl groups include vinyl and allyl. A suitable alkynyl group is acetylene or propargyl.

When used herein the term "halogen" means fluorine, chlorine, bromine and iodine. The most apt halogens are fluorine and chlorine of which fluorine is preferred, unless otherwise stated.

As used herein, the term "aryl" as a group or part of a group means an aromatic radical such as phenyl, biphenyl or naphthyl, wherein said phenyl, biphenyl or naphthyl group may be optionally substituted by one, two or three groups independently selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy, NO_2, cyano, SR^a, SOR^a, SO_2R^a, COR^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4}alkoxyC_{1-4}alkyl or $-O(CH_2)_mO-$. Preferably said phenyl, biphenyl or naphthyl group is optionally substituted by one or two substituents, especially none or one. Particularly preferred substituents include fluorine, chlorine, bromine, C_{1-4}alkyl (especially methyl), C_{1-4}alkoxy (especially methoxy), trifluoromethyl, trifluormethoxy or vinyl.

As used herein, the term "heterocyclyl" as a group or part of a group means a saturated, partially saturated or unsaturated heteroatom-containing ring-shaped radical, where the heteroatoms may be s lected from nitrogen,

oxygen and sulfur. Examples of saturated heterocyclyl radicals include N-linked saturated 3 to 6-membered heteromonocyclic groups containing 1 to 3 nitrogen atoms and optionally 1 oxygen or sulfur atom (for example, azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl or piperazinyl substituted on the nitrogen atom by a C_{1-4}alkyl group or a C_{2-4}alkyl group substituted by hydroxy or C_{1-2}alkoxy). Examples of saturated heterocyclyl radicals also include C-linked saturated 3 to 6-membered heteromonocyclic groups containing, for example, one oxygen atom (for instance, tetrahydrofuranyl or tetrahydropyranyl). Examples of partially saturated heterocyclyl radicals include N-linked partially saturated 3 to 6-membered heteromonocyclic groups containing 1 to 3 nitrogen atoms (for example, 3-pyrroline). Examples of unsaturated heterocyclyl radicals include heteroaromatic rings selected from pyrrolyl, furanyl, thienyl, pyridyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazolyl, oxadiazolyl, thiadiazolyl, triazinyl, tetrazolyl, indolyl, benzofuranyl, benzthiophenyl, benzimidazolyl, benzisoxazolyl, benzoxazolyl, benzthiazolyl or benzisothiazolyl.

Said saturated and partially saturated heterocyclyl radicals may be optionally substituted by one, two or three groups independently selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy, NO_2, cyano, oxo (=O), NR^aR^b, SR^a, SOR^a, SO_2R^a, COR^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4}alkoxyC_{1-4}alkyl, $-O(CH_2)_mO-$, $-OCH_2CH_2CH_2-$, $-CH_2OCH_2CH_2-$ or $-CH_2OCH_2C(O)-$. Preferably said saturated or partially saturated heterocyclyl radical is optionally substituted by one or two substituents, especially none or one. Particularly preferred substituents include fluorine, chlorine, bromine, C_{1-4}alkyl (especially methyl), C_{1-4}alkoxy (especially methoxy), trifluoromethyl, trifluoromethoxy, oxo, vinyl, C_{1-4}alkylamino (especially methylamino) or di(C_{1-4}alkyl)amino (especially dimethylamino).

Said unsaturated heterocyclyl radicals may be optionally substituted by one, two or three groups independently selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy, NO_2, cyano, NR^aR^b, SR^a, SOR^a, SO_2R^a, COR^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4}alkoxyC_{1-4}alkyl or $-O(CH_2)_mO-$. Preferably said unsaturated heterocyclyl is optionally substituted by one or two substituents, especially none or one. Particularly preferred

substituents include fluorine, chlorine, bromine, C_{1-4}alkyl (especially methyl), C_{1-4}alkoxy (especially methoxy), trifluoromethyl, trifluoromethoxy or vinyl.

As used herein, the term "carbocyclyl" as a group or part of a group means a 3 to 7-membered cycloalkyl radical such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, wherein said cycloalkyl radical may be optionally substituted by one, two or three groups independently selected from halogen, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxyC_{1-6}alkyl, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy, NO_2, cyano, SR^a, SOR^a, SO_2R^a, COR^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{1-4}alkoxyC_{1-4}alkyl or $-O(CH_2)_mO-$. Preferably said cycloalkyl radical is substituted by one or two substituents, especially one. Particularly preferred substituents include fluorine, chlorine, bromine, C_{1-4}alkyl (especially methyl), methoxy, hydroxyC_{1-4}alkyl (especially $C(CH_3)_2OH$), trifluoromethyl, trifluoromethoxy or vinyl.

Specific compounds within the scope of this invention include:

cis-(*RS*)-4-methanesulfonyloxy-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;

(*RS*)-1-{1-[(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)methoxy]ethyl]}-3,5-bis(trifluoromethyl)benzene;

(*RS*)-1-{1-[(4-oxo-1-phenylcyclohexyl)methoxy]ethyl}-3,5-bis(trifluoromethyl)benzene;

(*RS*)-β-[(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol;

(*RS*)-β-[(4-oxo-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol;

(*RS*)-4-oxo-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide;

(*RS*)-1-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)-3-[3,5-bis(trifluoromethyl)phenyl]propan-2-yl ethanoate;

(*RS*)-1-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)-3-[3,5-bis(trifluoromethyl)phenyl]propan-1-yl ethanoate;

(*RS*)-1-(8-ph nyl-1,4-dioxaspiro[4.5]decan-8-yl)-3-[3,5-bis(trifluoromethyl)phenyl]propan-2-ol;

RS)-4-{2-hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]propyl}-4-phenylcyclohexanone;

trans-(*RS*)-1-({4-[4-(4-fluorophenyl)piperidin-1-yl]-α-methyl-1-phenylcyclohexanemethoxy}methyl)-3,5-bis(trifluoromethyl)benzene;

cis-(*RS*)-1-({α-ethenyl-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanemethoxy}methyl)-3,5-bis(trifluoromethyl)benzene;

trans-(*RS*)-1-({α-ethenyl-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanemethoxy}methyl)-3,5-bis(trifluoromethyl)benzene;

trans-(*RS*)-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenyl-α-[3,5-bis(trifluoromethyl)phenylmethoxy]cyclohexaneethanol;

trans-(*RS*)-1-({α-ethyl-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanemethoxy}methyl)-3,5-bis(trifluoromethyl)benzene;

trans-1-[({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methoxy)methyl]-2-methoxybenzene;

trans-1-[({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methoxy)methyl]-2-(cyclopropoxy)-5-(trifluoromethoxy)benzene;

cis-(*RS*)-1-[1-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methoxy)ethyl]-3,5-bis(trifluoromethyl)benzene;

trans-(*RS*)-1-[1-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methoxy)ethyl]-3,5-bis(trifluoromethyl)benzene;

trans-(*RS*)-β-[(4-hydroxy-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol;

cis-(*RS*)-β-[(4-hydroxy-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol;

cis-(*RS*)-β-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methoxy)-3,5-bis(trifluoromethyl)benzeneethanol;

trans-(*RS*)-β-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methoxy)-3,5-bis(trifluoromethyl)benzeneethanol;

cis- and *trans*-(*RS*)-β-{[1-phenyl-4-(phenylmethylamino)cyclohexyl]methoxy}-3,5-bis(trifluoromethyl)benzeneethanol;

cis- and *trans*-(*RS*)-β-[(1-phenyl-4-(piperidin-1-yl)cyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol;

trans-(*RS*)-β-{[1-phenyl-4-(phenylmethylamino)cyclohexyl]methoxy}-3,5-bis(trifluoromethyl)benzeneethanol;

cis-(*RS*)-β-{[1-phenyl-4-(phenylmethylamino)cyclohexyl]methoxy}-3,5-bis(trifluoromethyl)benzeneethanol;

trans-(*RS*)-β-[(4-amino-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol;

cis-(*RS*)-β-[(4-amino-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol;

trans-(*RS*)-β-({4-[N-methyl(phenylmethyl)amino]-1-phenylcyclohexyl}methoxy)-3,5-bis(trifluoromethyl)benzeneethanol;

trans-(*RS*)-β-[(4-methylamino-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol;

trans-(*RS*)-β-[(4-{N-[2-(dimethylamino)acetyl]amino}-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol;

trans-(*RS,S*)-N-(1-{[α-hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy]methyl}-1-phenylcyclohexyl)-2-pyrrolidinecarboxamide;

cis- and *trans*-(*RS*)-β-[(1-phenyl-4-dimethylaminocyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol;

trans-(*RS*)-β-[(4-cyclopropylmethylamino-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol;

1,2-dihydro-5-{[N-(1-{[α-hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy]methyl}-1-phenylcyclohex-4-yl)methylamino]methyl}-3*H*-1,2,4-triazol-3-one;

cis-(*RS*)-methyl 1-(1-{[α-hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy]methyl}-1-phenylcyclohex-4-yl)piperidine-4-carboxylate;

trans-(*RS*)-methyl 1-(1-{[α-hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy]methyl}-1-phenylcyclohex-4-yl)piperidine-4-carboxylate;

trans-(*RS*)-1-(1-{[α-hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy]methyl}-1-phenylcyclohex-4-yl)piperidine-4-methanol;

trans-(*RS*)-1-(1-{[α-hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy]methyl}-1-phenylcyclohex-4-yl)piperidine-4-carboxylic acid;

trans-(*RS*)-1-(1-{[α-hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy]methyl}-1-phenylcyclohex-4-yl)-α,α-dimethylpiperidine-4-methanol;

trans-(*RS*)-1-(1-{[α-hydroxymethyl-3,5-bis(triflu romethyl)phenylmethoxy]methyl}-1-phenylcyclohex-4-yl)-N,N-dimethylpiperidine-4-carboxamide;

RS)-methyl (1-(1-{[α-hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy] methyl}-1-phenylcyclohex-4-ylidene)acetate;

cis- and *trans*-(*RS*)-methyl (1-(1-{[α-hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy]methyl}-1-phenylcyclohex-4-yl)acetate;

cis-(*RS*)-1-[2-(1-(1-{[α-hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy] methyl}-1-phenylcyclohex-4-yl)ethyl]pyrrolidine;

trans-(*RS*)-1-[2-(1-(1-{[α-hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy] methyl}-1-phenylcyclohex-4-yl)ethyl]pyrrolidine;

trans-(*RS*)-methyl α-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methoxy)-3,5-bis(trifluoromethyl)benzeneacetate;

trans-3,5-bis(trifluoromethyl)phenylmethyl 4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylate;

trans-(*RS*)-1-[3,5-bis(trifluoromethyl)phenyl]ethyl 4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylate;

trans-(*RS*)-2-hydroxy-2-[3,5-bis(trifluoromethyl)phenyl]ethyl 4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylate;

trans-(*RS*)-α-(hydroxymethyl)-[3,5-bis(trifluoromethyl)phenyl]methyl 4-[4-(4-fluorophenyl)piperidin-1-yl]-1-(phenyl)cyclohexanecarboxylate;

trans-(*RS*)-methyl α-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}carbonyloxy)-3,5-bis(trifluoromethyl)benzeneacetate;

cis-{4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methyl 3,5-bis(trifluoromethyl)benzoate;

trans-{4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methyl 3,5-bis(trifluoromethyl)benzoate;

cis-1-phenyl-4-(4-phenylpiperidin-1-yl)-N-{[3,5-bis(trifluoromethyl)phenyl] methyl}cyclohexanecarboxamide;

trans-1-phenyl-4-(4-phenylpiperidin-1-yl)-N-{[3,5-bis(trifluoromethyl)phenyl] methyl}cyclohexanecarboxamide;

trans-4-[4-(4-fluorophenyl)piperidin-1-yl]-N-{[3-(methoxy)phenyl]methyl}-1-phenylcyclohexanecarboxamide;

trans-(*RS*)-4-[4-(4-fluorophenyl)piperidin-1-yl]-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;

trans-(*R*)-4-[4-(4-fluorophenyl)piperidin-1-yl]-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;
trans-(*S*)-4-[4-(4-fluorophenyl)piperidin-1-yl]-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;
cis-(*RS*)-4-[4-(4-fluorophenyl)piperidin-1-yl]-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;
trans-N-methyl-1-phenyl-4-(4-phenylpiperidin-1-yl)-N-{[3,5-bis(trifluoromethyl)phenyl]methyl}cyclohexanecarboxamide;
trans-(*RS*)-4-[4-(4-fluorophenyl)piperidin-1-yl]-N-methyl-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;
trans-(*RS*)-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenyl-N-{2-hydroxy-1-[3,5-bis(trifluoromethyl)phenyl]}ethyl}cyclohexanecarboxamide;
trans-(*RS*)-4-(1,4-dioxa-8-azaspiro[4.5]decane-8-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide;
trans-(*RS*)-4-(4-oxopiperidin-1-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide;
trans-(*RS*)-4-(4-hydroxypiperidin-1-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide;
trans-(*RS*)-4-(but-3-enylamino)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide;
trans-(*RS*)-4-(4-hydroxy-4-phenylpiperidin-1-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide;
trans-(*RS*)-4-(1,2,3,6-tetrahydro-4-phenylpyridin-1-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide;
trans-(*RS*)-4-(1,2,3,6-tetrahydro-4-methylpyridin-1-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide;
trans-(*RS*)-4-(4-hydroxy-4-(phenylethyl)piperidin-1-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide;
trans-(*RS*)-4-[(phenylmethyl)amino]-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;
cis-(*RS*)-4-[(phenylmethyl)amino]-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;

trans-(*RS*)-4-[N-methyl(phenylmethyl)amino]-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;

trans-(*RS*)-4-methylamino-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;

trans-(*RS*)-4-amino-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;

trans-(*RS*)-4-(dimethylamino)-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;

trans-(*RS*)-4-[4-(phenylbutyl)amino]-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;

trans-(*RS*)-4-[N-methyl-4-(phenylbutyl)amino]-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;

trans-(*RS*)-4-acetylamino-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;

trans-(*RS*)-4-[(1-oxo-4-phenylbutyl)amino]-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;

cis- and *trans*-(*RS*)-1,1-dimethylethyl 4-[1-({1-[3,5-bis(trifluoromethyl)phenyl]ethylamino}carbonyl)-1-phenylcyclohex-4-yl]-1-piperazinecarboxylate;

trans-(*RS*)-4-[4-(phenylmethyl)piperazin-1-yl]-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;

trans-(*RS*)-4-(piperazin-1-yl)-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;

trans-(*RS*)-4-(4-methylpiperazin-1-yl)-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;

trans-(*RS*)-4-(4-acetylpiperazin-1-yl)-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;

trans-(*RS*)-4-(aminomethyl)-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;

trans-(*RS*)-4-(N,N-dimethylaminomethyl)-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;

trans-(*RS*)-4-[(piperidin-1-yl)methyl]-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;

trans-(*RS*)-4-[(morpholin-4-yl)methyl]-N-{1-[3,5-bis(trifluoromethyl)phenyl] ethyl}-1-phenylcyclohexanecarboxamide;

trans-(*RS*)-4-({N-[2-(dimethylamino)acetyl]}aminomethyl)-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;

trans-(*RS*)-4-(1*H*-1,2,3-triazol-1-yl)-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;

trans-N-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methyl)-3,5-bis(trifluoromethyl)benzenecarboxamide;

trans-N-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methyl)-2-(methoxy)benzenemethanamine;

trans-N-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methyl)-3,5-bis(trifluoromethyl)benzenemethanamine;

cis-N-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methyl)-3,5-bis(trifluoromethyl)benzenemethanamine;

trans-N-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methyl)-N-methyl-3,5-bis(trifluoromethyl)benzenemethanamine;

cis- and *trans*-N-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methyl)-N-{[3,5-bis(trifluoromethyl)phenyl]methyl}acetamide;

trans-(*RS*)-N-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methyl)-α-methyl-3,5-bis(trifluoromethyl)benzenemethanamine;

trans-(*RS*)-α-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methylamino)-3,5-bis(trifluoromethyl)benzeneethanol;

trans-(*RS*)-α-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methylamino)-3,5-bis(trifluoromethyl)benzeneethanamine;

cis- and *trans*-(*E*)-4-(4-fluorophenyl)-1-(4-phenyl-4-{3-[3,5-bis(trifluoromethyl)phenyl]prop-1-enyl}cyclohexyl)piperidine;

cis- and *trans*-(*E*)-4-(4-fluorophenyl)-1-(4-phenyl-4-{3-[3,5-bis(trifluoromethyl)phenyl]propyl}cyclohexyl)piperidine;

cis- and *trans*-(*RS*)-4-(4-fluorophenyl)-1-(4-{2-hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]propyl}-4-phenylcyclohexyl)piperidine;

cis- and *trans*-(*RS*)-4-(4-fluorophenyl)-1-(4-{2-oxo-3-[3,5-bis(trifluoromethyl)phenyl]propyl}-4-phenylcyclohexyl)piperidine;

1-{[(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)methoxy]methyl}-3,5-bis(trifluoromethyl)benzene;

1-({[4-oxo-1-phenylcyclohexyl]methoxy}methyl)- 3,5-bis(trifluoromethyl)benzene;

cis-1-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanemethoxy}methyl)-3,5-bis(trifluoromethyl)benzene;

trans-1-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanemethoxy}methyl)-3,5-bis(trifluoromethyl)benzene;

(RS)-4-methylene-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl} cyclohexanecarboxamide;

cis-(*RS*)-4-(hydroxymethyl)-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;

trans-(*RS*)-4-(hydroxymethyl)-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide;

and pharmaceutically acceptable salts thereof.

In a further aspect of the present invention, the compounds of formula (I) may be prepared in the form of a pharmaceutically acceptable salt, especially an acid addition salt.

For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or sulphuric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate

acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

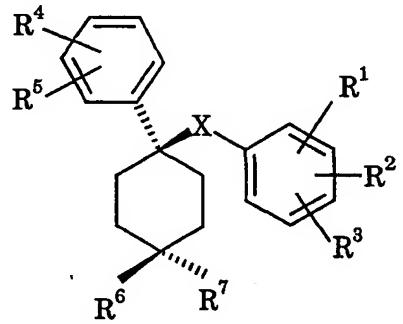
The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible *in vivo* into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

A prodrug may be a pharmacologically inactive derivative of a biologically active substance (the "parent drug" or "parent molecule") that requires transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. The transformation *in vivo* may be, for example, as the result of some metabolic process, such as chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulphate ester, or reduction or oxidation of a susceptible functionality.

The present invention includes within its scope solvates of the compounds of formula (I) and salts thereof, for example, hydrates.

The compounds according to the invention have one or more asymmetric centres, and may accordingly exist both as enantiomers and as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The preferred compounds of the formula (I) and (Ia) will have the stereochemistry of the 1- and 4-positions as shown in formula (Ib)



(Ib)

It will be appreciated that the preferred definitions of the various substituents recited herein may be taken alone or in combination and, unless otherwise stated, apply to the generic formula for compounds of the present invention as well as to the preferred classes of compound represented by formula (Ia) and formula (Ib).

The present invention further provides pharmaceutical compositions comprising one or more compounds of formula (I) in association with a pharmaceutically acceptable carrier or excipient.

Preferably the compositions according to the invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or administration by inhalation or insufflation. Oral compositions such as tablets, pills, capsules or wafers are particularly preferred.

A more detailed description of pharmaceutical compositions that are suitable for the formulation of compounds of the present invention is disclosed in US patent No. 6,071,927, the content of which is incorporated herein by reference (see in particular, column 8, line 50 to column 10, line 4).

The present invention further provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), which process comprises bringing a compound of formula (I) into association with a pharmaceutically acceptable carrier or excipient.

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity. A comprehensive listing of clinical conditions, uses and methods of treatment for which the compounds of the present invention will be useful is disclosed in US patent No. 6,071,927, the content of which is incorporated herein by reference (see, in particular, column 10, line 14 to column 22, line 18).

In particular, the compounds of the present invention are useful in the treatment of a variety of disorders of the central nervous system. Such disorders include mood disorders, such as depression or more particularly depressive disorders, for example, single episodic or recurrent major depressive disorders and dysthymic disorders, or bipolar disorders, for example, bipolar I disorder,

bipolar II disorder and cyclothymic disorder; and anxiety disorders, such as panic disorder with or without agoraphobia, agoraphobia without history of panic disorder, specific phobias, for example, specific animal phobias, social phobias, obsessive-compulsive disorder, stress disorders including post-traumatic stress disorder and acute stress disorder, and generalised anxiety disorders.

The compounds of the present invention are also particularly useful in the treatment of nociception and pain. Diseases and conditions in which pain predominates, include soft tissue and peripheral damage, such as acute trauma, osteoarthritis, rheumatoid arthritis, musculo-skeletal pain, particularly after trauma, spinal pain, myofascial pain syndromes, headache, migraine, episiotomy pain, and burns.

The compounds of the present invention are also particularly useful in the treatment of respiratory diseases, particularly those associated with excess mucus secretion, such as chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, adult respiratory distress syndrome, and bronchospasm; in the treatment of inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis, pruritis and sunburn; and in the treatment of allergic disorders such as eczema and rhinitis.

The compounds of the present invention are also particularly useful in the treatment of gastrointestinal (GI) disorders, including inflammatory disorders and diseases of the GI tract such as ulcerative colitis, Crohn's disease and irritable bowel syndrome.

The compounds of the present invention are also particularly useful in the treatment of emesis, including acute, delayed or anticipatory emesis, such as emesis induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, motion, surgery, migraine, and variations in intercranial pressure. Most especially, the compounds of formula (I) are of use in the treatment of emesis induced by antineoplastic (cytotoxic) agents, including those routinely used in cancer chemotherapy; by radiation including radiation therapy such as in the treatment of cancer; and in the treatment of post-operative nausea and vomiting.

The excellent pharmacological profile of the compounds of the present invention offers the opportunity for their use in therapy at low doses thereby minimising the risk of unwanted side effects.

In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day.

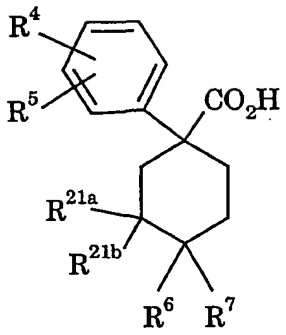
For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

In the treatment of emesis, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially 0.01 to 3 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

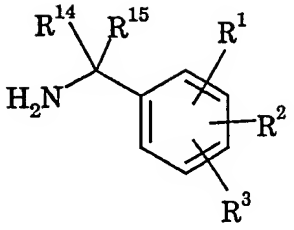
In the treatment of psychiatric disorders, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially 0.01 to 3 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It will be appreciated that the amount of a compound of formula (I) required for use in any treatment will vary not only with the particular compounds or composition selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician.

According to a general process (A), compounds of formula (I), in which X is $-C(O)N(R^{13})CR^{14}R^{15}-$, may be prepared by the reaction of a compound of formula (II) with a compound of formula (III)



(II)



(III)

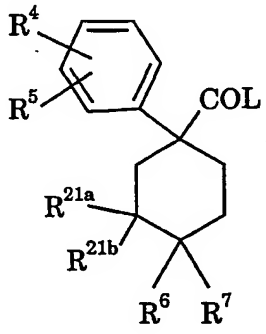
in the presence of a base and a coupling reagent.

Suitable bases of use in the reaction include tertiary amines, for example, triethylamine.

Suitable coupling reagents include any of the coupling reagents commonly used in peptide synthesis. A preferred coupling reagent is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC). Preferably the coupling reaction is effected in the presence of 1-hydroxybenzotriazole hydrate (HOBT).

The reaction is conveniently effected in a suitable organic solvent such as, for example, dimethylformamide.

According to an alternative general process (B), compounds of formula (I), in which X is $-C(O)N(R^{13})CR^{14}R^{15}-$, may be prepared by the reaction of an amine of formula (III) with an activated carboxylic acid derivative of formula (IV)



(IV)

where L is a leaving group.

Suitable activated carboxylic acid derivatives represented in formula (IV) include acyl halides (e.g. acid chlorides) and acid anhydrides including mixed anhydrides (e.g. acid formic anhydride). These activated derivatives may be formed from the corresponding acid of formula (II) by well known procedures. For example, acid chlorides may be prepared by reaction with phosphorus pentachloride, thionyl chloride or oxalyl chloride and acid anhydrides may be prepared by reaction with an appropriate acid anhydride (e.g. trifluoroacetic anhydride), an acid chloride (e.g. acetyl chloride), an alkyl or aralkyl haloformate (e.g. ethyl or benzyl chloroformate) or methanesulphonyl chloride.

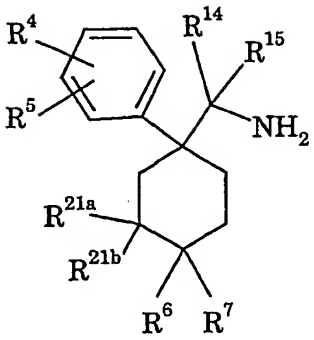
A particularly preferred reagent for activating the carboxylic acid group is bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl).

Activated carboxylic acid derivatives of formula (IV) may also be prepared in situ by reaction of the corresponding acids of formula (II), with a coupling reagent such as carbonyldiimidazole, dicyclohexylcarbodiimide or diphenylphosphorylazide.

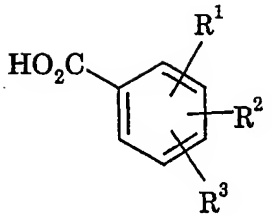
The conditions under which the activated carboxylic acid derivatives of formula (IV) are formed and subsequently reacted with the amines of formula (III) will depend upon the nature of the activated derivative. However, in general the reaction between the compounds (III) and (IV) may be carried out in a non-aqueous medium such as, for example, dimethylformamide, tetrahydrofuran, acetonitrile or a halogenated hydrocarbon such as dichloromethane at a temperature within the range -25°C to +150°C. The reaction may optionally be carried out in the presence of a base such as triethylamine or pyridine and the base may also be used as the solvent for reaction.

Where acid chlorides are used, the reaction may be carried out using the Schotten-Baumann technique in the presence of a suitable base, for example, aqueous sodium hydroxide, conveniently at a temperature between 0°C and 100°C, for example, room temperature.

According to another general process (C), compounds of formula (I), in which X is $-CR^{14}R^{15}N(R^{13})C(O)-$, may be prepared by the reaction of a compound of formula (V) with a compound of formula (VI) or an activated derivative thereof



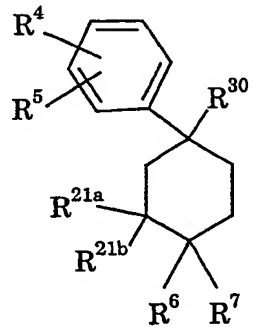
(V)



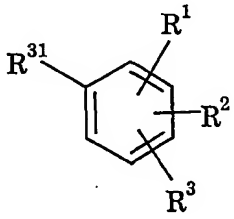
(VI)

using the methods described in processes (A) and (B), above.

According to another general process (D), compounds of formula (I), in which X is $-CR^{14}R^{15}N(R^{13})CR^{16}R^{17}-$, may be prepared by the reaction of a compound of formula (VII) with a compound of formula (VIII)



(VII)



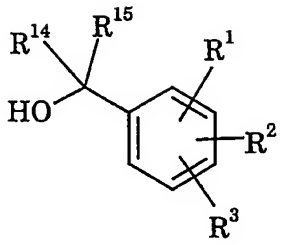
(VIII)

(wherein R^{30} is $-CR^{14}R^{15}NH_2$ and R^{31} is CHO, or R^{30} is CHO and R^{31} is $-CR^{16}R^{17}NH_2$) in the presence of a reducing agent.

Suitable reducing agents for use in this reaction include, for example, sodium cyanoborohydride or sodium triacetoxyborohydride.

The reaction is conveniently effected in a suitable solvent such as a halogenated hydrocarbon, for example, 1,2-dichloroethane, an alcohol, for example, methanol, acetic acid or a mixture thereof.

According t another general process (E), compounds of formula (I), in which X is $-C(O)OCR^{14}R^{15}-$, may be prepared by the reaction of an activated carboxylic acid derivative (IV) with a compound of formula (IX)



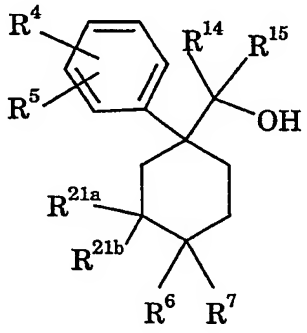
(IX)

in the presence of a base.

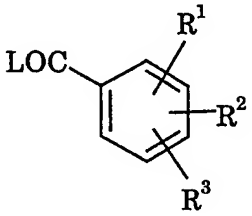
Suitable bases of use in the reaction include aromatic amines such as pyridine or 4-(dimethylamino)pyridine (DMAP).

The reaction is conveniently effected in a suitable aprotic solvent such as, for example, dimethylformamide, or a halogenated hydrocarbon, for example, dichloromethane, or a mixture thereof.

According to another general process (F), compounds of formula (I), in which X is $-CR^{14}R^{15}OC(O)-$, may be prepared by the reaction of a compound of formula (X) with a compound of formula (XI)



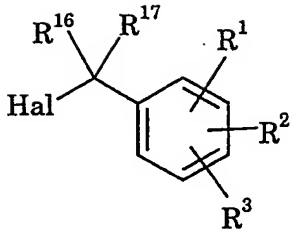
(X)



(XI)

(provided that R^{21a} is not hydroxy) using a method described in process (E) above.

According to another general process (G), compounds of formula (I), in which X is $-CR^{14}R^{15}OCR^{16}R^{17}-$, may be prepared by reacting a compound of formula (X) with a compound of formula (XII)

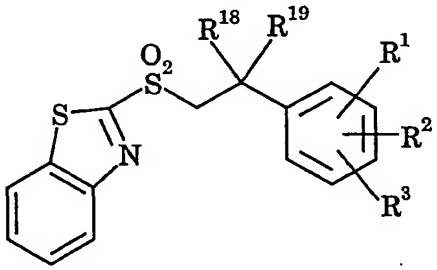


(XII)

(wherein Hal is a halogen atom such as chlorine, iodine or, preferably, bromine), in the presence of a base such as sodium hydride.

The reaction is conveniently effected in a suitable aprotic solvent such as, for example, dimethylformamide.

According to another general process (H), compounds of formula (I), in which X is $-CH=CHCR^{18}R^{19}-$, may be prepared by the reaction of a compound of formula (VII) where R^{30} is CHO with a compound of formula (XIII)

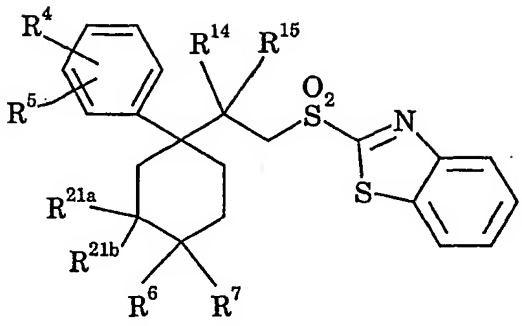


(XIII)

in the presence of lithium hexamethyldisilazide.

The reaction is conveniently effected in a suitable aprotic solvent such as an ether, for example, tetrahydrofuran, at a reduced temperature, for example, at about -78°C.

According to another general process (J), comp unds f formula (I), in which X is $-CR^{14}R^{15}CH=CH-$, may be prepared by the reaction of a compound of formula (VIII) wherein R^{31} is CHO with a compound of formula (XIV)



(XIV)

using the method described in process (H), above.

It will be appreciated that compounds of formula (I) may also be prepared from other compounds of formula (I) by a variety of interconversion processes.

Thus, according to general process (K.1), compounds of formula (I) in which X is $-CR^{14}R^{15}N(R^{13})CR^{16}R^{17}-$, may be prepared by the interconversion of a compound of formula (I) in which X is either $-C(O)N(R^{13})CR^{14}R^{15}-$ or $-CR^{14}R^{15}N(R^{13})C(O)-$, by reaction with a reducing agent.

Suitable reducing agents for use in this reaction include sodium borohydride or borane.tetrahydrofuran complex.

The reaction is conveniently effected in a solvent such as an ether, for example, tetrahydrofuran.

According to another general process (K.2), compounds of formula (I) in which X is $-CR^{14}R^{15}OCH(CH_3)-$ or $-CH(CH_3)OCR^{14}R^{15}-$, may be prepared by interconversion of a compound of formula (I) in which X is $-CR^{14}R^{15}OC(O)-$ or $-C(O)OCR^{14}R^{15}-$, respectively, by reaction with dimethyltitanocene in toluene followed by reduction using, for instance, catalytic hydrogenation conditions, for example, hydrogenation in the presence of palladium hydroxide on carbon, in a suitable solvent such as an ester, for example, ethyl acetate.

According to another general process (K.3), compounds of formula (I) in which X is $-CR^{14}R^{15}OCH(CH_2OH)-$ or $-CH(CH_2OH)OCR^{14}R^{15}-$, may be prepared by interconversion of a compound of formula (I) in which X is $-CR^{14}R^{15}OC(O)-$ or $-C(O)OCR^{14}R^{15}-$, respectively, by reaction with dimethyltitanocene in toluene followed by reduction using, for instance, a reducing agent such as

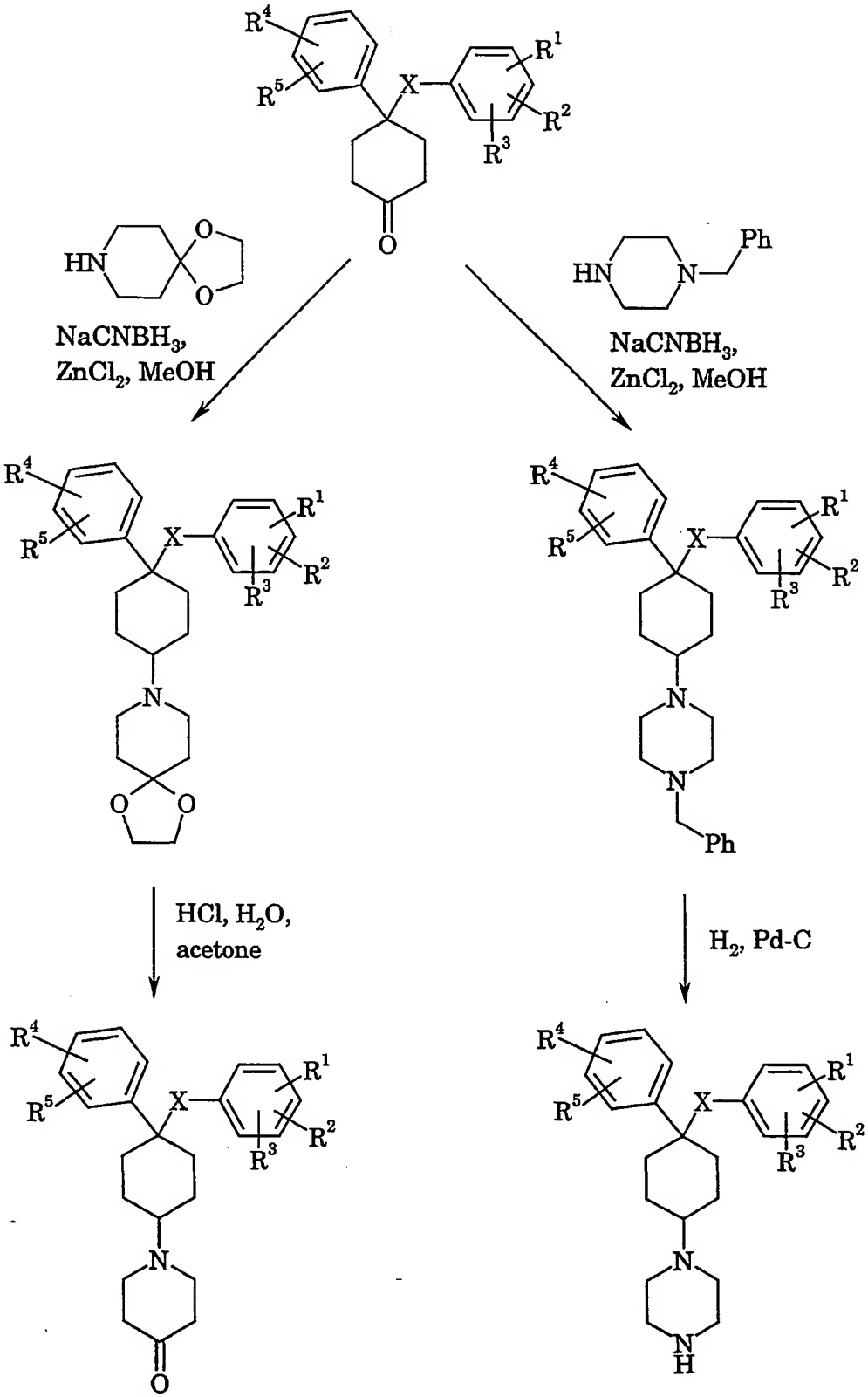
borane.tetrahydrofuran complex, followed by treatment with hydrogen peroxide in the presence of a base such as sodium hydroxide.

According to another general process (K.4), compounds of formula (I) in which X is -$CR^{14}R^{15}CR^{16}R^{17}CR^{18}R^{19}$-, may be prepared by interconversion of a compound of formula (I) in which X is -CR^{14}=$CR^{16}CR^{18}R^{19}$- or -$CR^{14}R^{15}CR^{16}$=CR^{18}-, by reduction using, for instance, catalytic hydrogenation conditions, for example, hydrogenation in the presence of palladium hydroxide on carbon, in a suitable solvent such as an alcohol, for example, methanol.

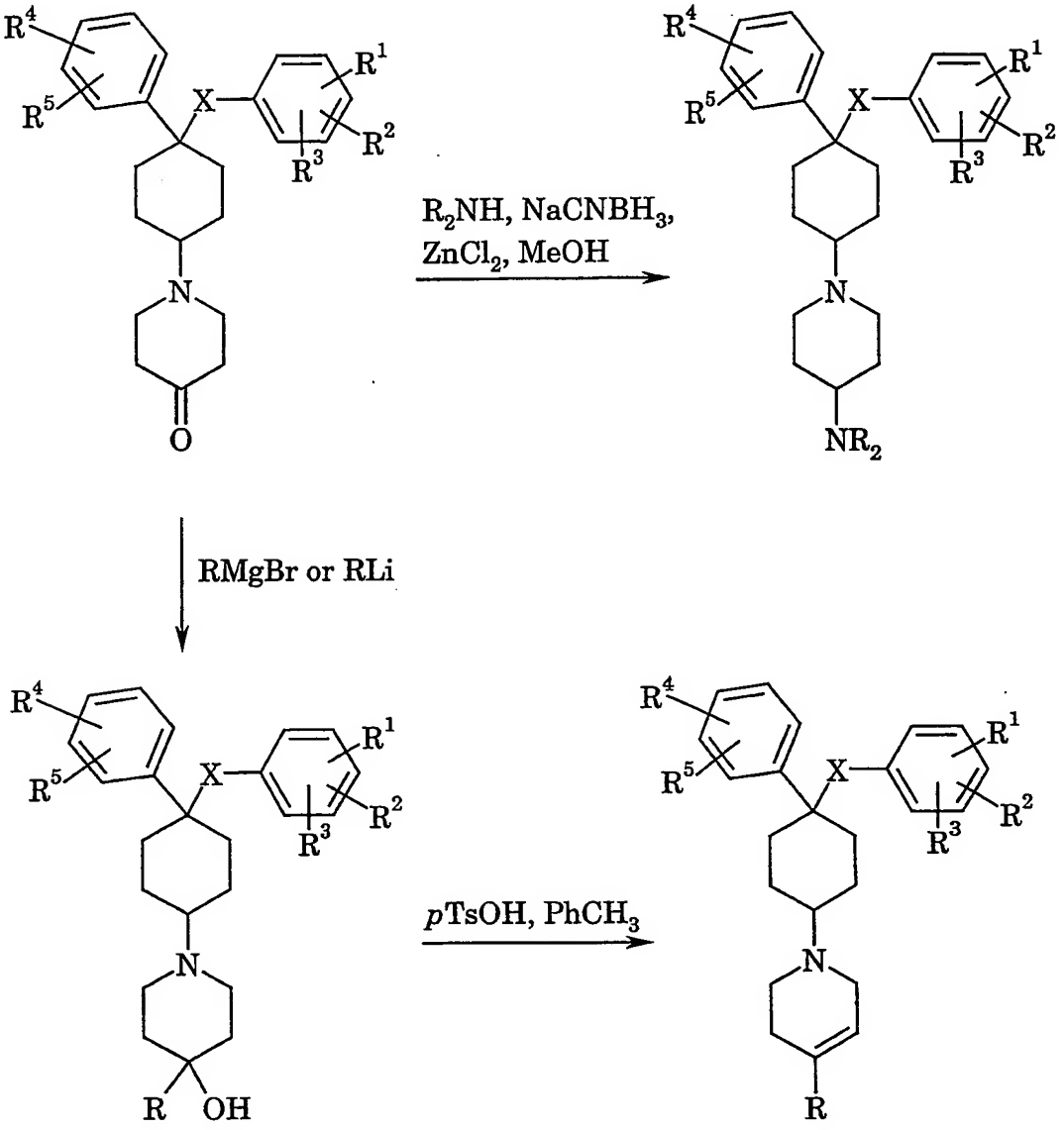
According to another general process (K.5), compounds of formula (I) in which R^7 is –$(CH_2)_nNR^8R^9$ (where n is zero) may be prepared by interconversion of a compound of formula (I) in which R^6 and R^7 together represent =O, by reaction with an appropriate amine, R^8R^9NH, in the presence of sodium cyanoborohydride and a Lewis acid, for example, zinc chloride, in a solvent such as an alcohol, for example, methanol, or in the presence of sodium triacetoxyborohydride in a solvent such as a halogenated hydrocarbon, for example, 1,2-dichloroethane.

Yet further interconversion reactions that may be effected using conventional procedures are shown in the following Scheme 1. The methods depicted in Scheme 1 are not exhaustive and illustrate just some of the possible routes to further compounds of formula (I).

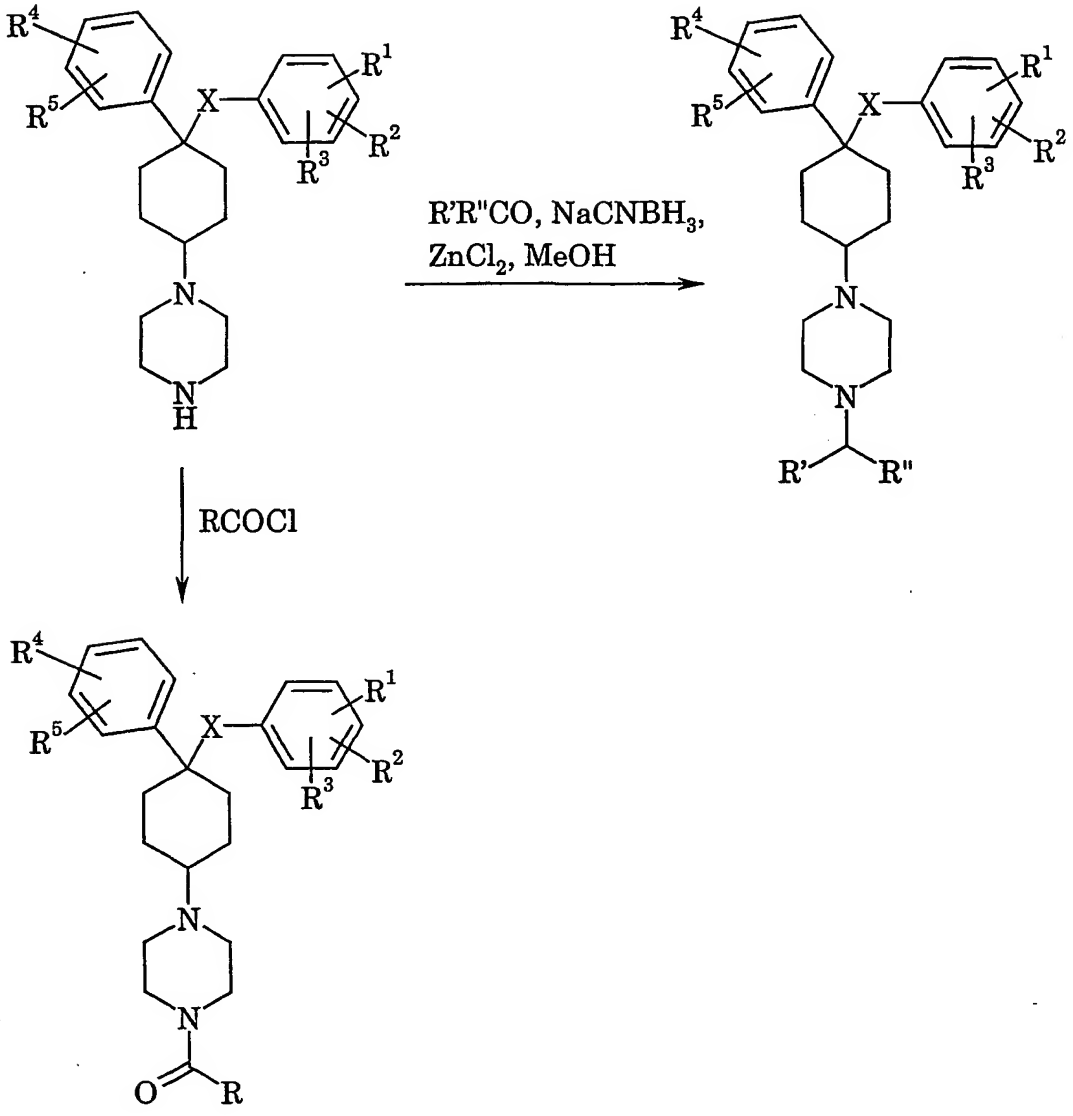
Scheme 1


NaCNBH3,
ZnCl2, MeOH
NaCNBH3,
ZnCl2, MeOH
HCl, H2O,
acetone
H2, Pd-C

Scheme 1 (continued)



Scheme 1 (continued)



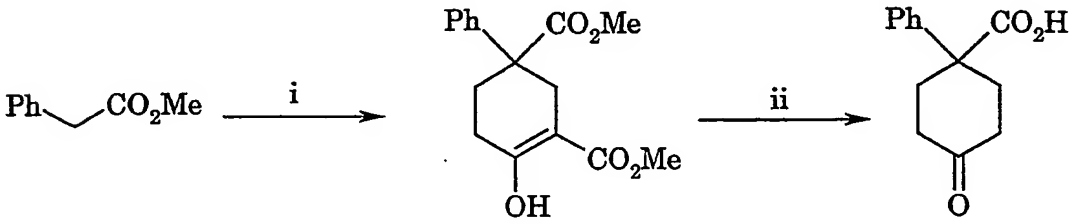
It will be appreciated that reference to R, R' and R" in Scheme 1 refers to suitable substituents within the scope of the definitions of formula (I), insofar as said substituents are compatible with the reaction conditions described in Scheme 1.

Preferably, where R^{21a} is halogen or hydroxy, or R^{21a} and R^{21b} both represent fluorine or together represent oxo (=O), such substituents are introduced at a late stage by conventional methodology. It will be appreciated, however, that where such substituents are compatible with the reactions

described above, then such groups may be present, even if not depicted in the above formulae.

Further details of suitable procedures for the preparation of compounds of formula (I) will be found in the accompanying Examples.

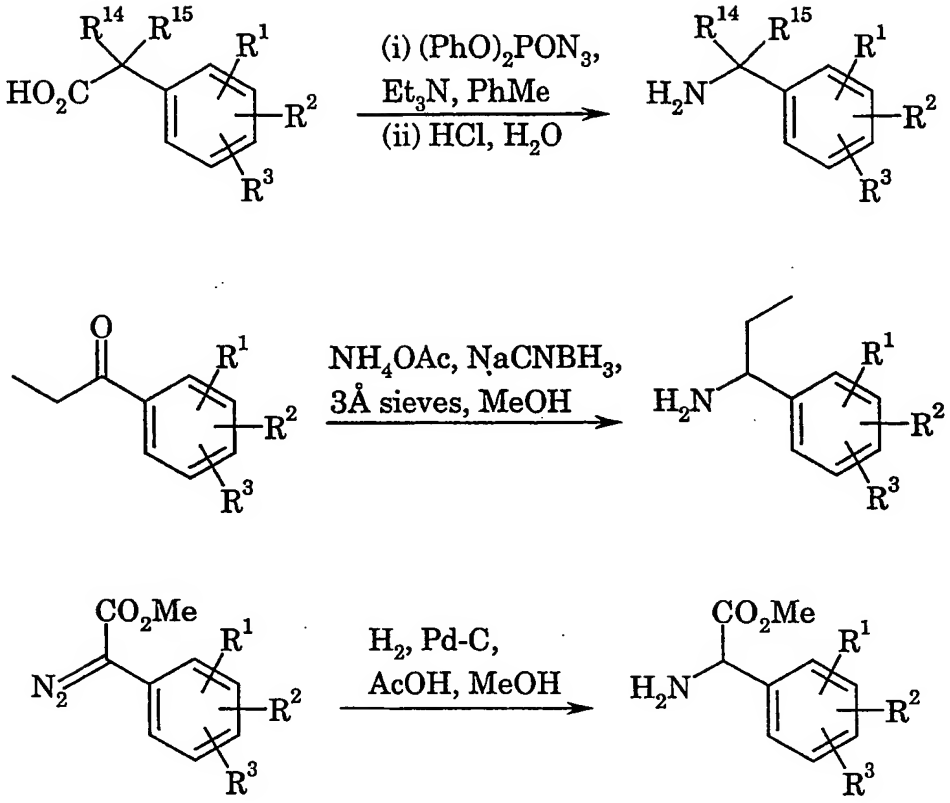
Compounds of formula (II) may be prepared by conventional methods. Thus for example, a compound of formula (II) wherein R^6 and R^7 together represent =O may be prepared according to the following two-step procedure or by methods analogous thereto:



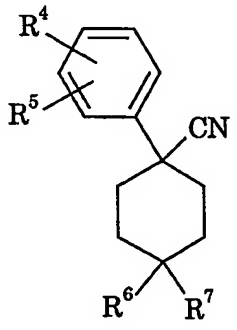
In step (i), methyl phenyl acetate is treated with a base such as sodium hydride and reacted with methyl acrylate. The reaction is conveniently effected in a solvent such as dimethylformamide at a temperature between 0°C and room temperature. In step (ii), selective decarboxylation is effected using, for example, lithium hydroxide. The reaction is conveniently effected in a solvent or mixture of solvents such as an alcohol, for example, methanol, an ether, for example, tetrahydrofuran, and water. The desired carboxylic acid is obtained by acid hydrolysis of the ester using, for example, a mineral acid such as hydrochloric acid.

Compounds of formula (III) are either known compounds or may be prepared by conventional methods. Examples of suitable methods include, but are not limited to, the methods shown in Scheme 2.

Scheme 2



Compounds of formula (V) in which R^{14} and R^{15} are both hydrogen may be prepared from the corresponding carbonitrile compound of formula (XV)



(XV)

by treatment with a reducing agent such as lithium aluminium hydride. The reaction is conveniently effected at room temperature in a solvent such as an ether, for example, diethyl ether.

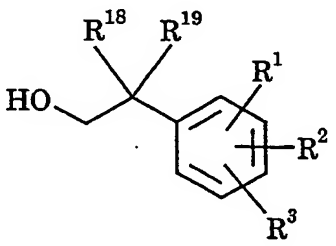
Similarly, compounds of formula (VII) in which R^{30} is CHO may be prepared, for example, by reduction of the corresponding carbonitrile of formula (XV) using a suitable reducing agent such as diisobutylaluminium hydride (DIBAL-H). The reaction is conveniently effected in a solvent such as a halogenated hydrocarbon, for example, dichloromethane, or a hydrocarbon, for example, hexane, or a mixture thereof.

Compounds of formula (IX) are either known compounds or may be prepared by conventional methods, for instance, reduction of the corresponding carboxylic acid using, for example, lithium aluminium hydride at room temperature in a solvent such as as ether, for example, diethyl ether.

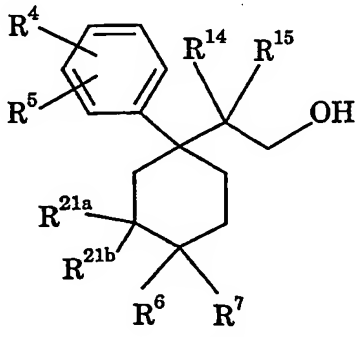
Similarly, compounds of formula (X) may be prepared by reduction of the corresponding carboxylic acid or, more preferably, the corresponding aldehyde of formula (VII) in which R^{30} is CHO. Suitable reducing agents include diisobutylaluminium hydride, lithium aluminium hydride or, more preferably, sodium borohydride. The reaction is conveniently effected in a solvent such as an ether, for example, diethyl ether, a halogenated hydrocarbon, for example dichloromethane, or a hydrocarbon, for example, hexane, or a mixture thereof.

Compounds of formula (XI) may be prepared from the corresponding carboxylic acid of formula (VI) using methods analogous to those described herein for the synthesis of compounds of formula (IV).

Compounds of formulae (XIII) and (XIV) may be prepared by conventional methods, in particular by the reaction of a compound of formula (XVI) or (XVII), respectively



(XVI)



(XVII)

(provided that R^{21a} is not hydroxy) with 2,2′-dithiobis(benzothiazole) in the presence of tributylphosphine to afford the ethylthiobenzothiazole which is subsequently oxidised using, for example, oxone. The benzothiazole step is conveniently effected in an aprotic solvent such as an ether, for example, tetrahydrofuran, whilst the oxidation step is conveniently effected in a solvent such as a halogenated hydrocarbon, for example, chloroform.

Compounds of formulae (VI), (XII), (XV) and (XVI) are either known compounds or may be prepared by conventional methods, for instance, by methods analogous to those described herein.

Compounds of formula (I) in which the ring A is a pyridyl ring may be prepared in an analogous manner to the methods described above, replacing the phenyl ring depicted in the above formulae as appropriate.

It will be appreciated that the general methodology described above may be adapted, using methods that are readily apparent to one of ordinary skill in the art, in order to prepare further compounds of the present invention.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The exemplified compounds of this invention were tested by the methods set out at pages 36 to 39 of International Patent Specification No. WO 93/01165. The compounds were found to be active with IC_{50} at the NK_1 receptor of less than 100nM on said test method.

The following non-limiting Examples serve to illustrate the preparation of compounds of the present invention:

DESCRIPTION 1

Dimethyl 4-Oxo-1-phenyl-1,3-cyclohexanedicarboxylate

Sodium hydride (60% in mineral oil, 35.8 g, 1.49 mol) was washed with hexane to remove the mineral oil, suspended in dimethylformamide (400 mL) and cooled to 0 °C. Methyl phenyl acetate (42 mL, 0.3 mol) was added slowly with stirring. Methyl acrylate (59 mL, 0.65 mol) was added dropwise over 2 hours at 0 °C and the mixture was stirred at room temperature overnight. Aqueous ammonium chloride (saturated) was added and the mixture was extracted with dichloromethane (2 x 700 mL). The combined organic fractions were washed with water (5 x 500 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with isohexane/Et_2O (80:20) and the residue was triturated with isohexane/Et_2O (50:50). The solid was collected and dried *in vacuo* to give the title compound as colorless crystals (30 g, 35%). ^{1}H NMR (400MHz, $CDCl_3$) δ 12.11 (1H, s), 7.36-7.25 (5H, m), 3.81 (3H, s), 3.64 (3H, s), 3.08 (1H, d, *J* 16.1 Hz), 2.73 (1H, d, *J* 16.1 Hz), 2.26-2.37 (2H, m), and 2.22-2.17 (2H, m).

DESCRIPTION 2

4-Oxo-1-phenylcyclohexanecarboxylic Acid

Lithium hydroxide monohydrate (11.08 g, 264 mmol) was added to a suspension of dimethyl 4-oxo-1-phenyl-1,3-cyclohexanedicarboxylate (Description 1, 25.5 g, 87.9 mmol) in methanol (250 mL), water (83 mL) and tetrahydrofuran (83 mL) and the mixture was heated under reflux for 3 days. The mixture was cooled and the tetrahydrofuran and methanol were evaporated under reduced pressure. The pH was adjusted to 1 with hydrochloric acid (5M) and the mixture was extracted with dichloromethane. The combined organic fractions were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound as a light yellow solid (19 g, 99%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.50-7.29 (5H, m), 2.29-2.73 (2H, m), 2.62-2.55 (2H, m), 2.47-2.41 (2H, m), and 2.35-2.27 (2H, m).

DESCRIPTION 3

(*RS*)-1-[3,5-Bis(trifluoromethyl)phenyl]-1,2-ethanediol

Osmium tetroxide (2.5 wt% solution in 2-methyl-2-propanol, 1 mL) was added to a mixture of 1-ethenyl-3,5-bis(trifluoromethyl)benzene (1.85 g, 7.74 mmol) and N-methylmorpholine-N-oxide (1.13 g, 9.67 mmol) in tetrahydrofuran (35 mL) and water (15 mL) and the mixture was stirred at room temperature for 18 hours. Aqueous sodium bisulfite (saturated, 30 mL) was added and the tetrahydrofuran was evaporated under reduced pressure. The mixture was extracted with ethyl acetate (2 x 100 mL) and the combined organic fractions were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give the title compound

(2.09 g, 98%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.86 (2H, s), 7.82 (1H, s), 4.97 (1H, dd, *J* 8.0, 4.0 Hz), 3.87 (1H, dd, *J* 11.0, 4.0 Hz), and 3.66 (1H, dd, *J* 8.0, 11.0 Hz).

DESCRIPTION 4

(*RS*)-1-[3,5-Bis(trifluoromethyl)-α-{[2-(trimethylsilyl)ethoxy]methoxymethyl} benzenemethanol

N-Ethyl-N,N-diisopropylamine (465 µl, 2.67 mmol) was added over 2 minutes, to a solution of (*RS*)-1-[3,5-bis(trifluoromethyl)phenyl]-1,2-ethanediol (Description 3, 488 mg, 1.78 mmol) and [2-(chloromethoxy)ethyl]trimethylsilane (315 µl, 1.78 mmol) in dichloromethane (3 mL) and the mixture was stirred at room temperature for 4 hours, then at 50 °C for 1 hour. The mixture was cooled and dichloromethane (20 mL) and water (20 mL) were added. The layers were separated and the aqueous layer was extracted with dichloromethane (10 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with isohexane/EtOAc (90:10) to give the title compound (352 mg, 49%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.86 (2H, s), 7.79 (1H, s), 4.96 (1H, m), 4.73 (2H, s), 3.87 (1H, dd, *J* 11.1, 3.0 Hz), 3.73 (1H, br s), 3.61 (3H, m), 0.93 (2H, t, *J* 8.5 Hz), and 0.02 (9H, s).

DESCRIPTION 5

(*RS*)-α-Methyl-3,5-bis(trifluoromethyl)benzenemethanamine

O-Methylhydroxylamine hydrochloride (19.57 g, 234 mmol) was added to a solution of 1-[3,5-bis(trifluoromethyl)phenyl]ethanone (50 g, 195 mmol), and sodium acetate (31.9 g, 234 mmol) in ethanol (450 mL) and water (150 mL) and the mixture was heated under reflux for 18 hours. The mixture was cooled, water (1000 mL) was added and the mixture was extracted with diethyl ether. The combined organic fractions were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (100 mL), cooled to 0 °C and borane-tetrahydrofuran complex (1M in tetrahydrofuran, 730 mL) was added. The mixture was heated under reflux for 18 hours, cooled and hydrochloric acid (5M, 500 mL) was added slowly. The tetrahydrofuran was evaporated under reduced pressure and the mixture was basified with aqueous sodium hydroxide (4M). The mixture was extracted with ether and the combined organic fractions were washed with aqueous sodium hydroxide (4M) and dried ($MgSO_4$). and ethereal hydrogen chloride (400 mL, 400 mmol) was added. The solid was collected, washing with diethyl ether, and dried *in vacuo* to give (RS)-*α-methyl-3,5-bis(trifluoromethyl)benzenemethanamine hydrochloride* as a

colorless solid (48.2 g, 100%). ^{1}H NMR (400MHz, CD_3OD) δ 8.13 (2H, s), 8.07 (1H, s), 4.73 (1H, q, *J* 6.8 Hz), 3.31 (2H, d, *J* 1.4 Hz), and 1.69 (3H, d, *J* 6.8 Hz). m/z (ES^+) 258 (M+1).

A sample was suspended in aqueous sodium hydroxide (4M) and extracted with ether. The combined organic fractions were washed with aqueous sodium hydroxide (4M), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound as a colorless oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.85 (2H, s), 7.76 (1H, s), 4.30 (1H, q, *J* 6.6 Hz), 1.74 (2H, br s), and 1.42 (3H, d, *J* 6.6 Hz). m/z (ES^+) 258 (M+1).

DESCRIPTION 6

(*RS*)-2-Methoxy-α-methylbenzenemethanamine Hydrochloride

Sodium cyanoborohydride (2.46 g, 39.1 mmol) was added to a mixture of 1-(2-methoxyphenyl)ethanone (5.87 g, 39.1 mmol), ammonium acetate (30 g, 391 mmol) and 3Å molecular sieves (20 g) in methanol (200 mL) and the mixture was stirred at room temperature for 3 days. The mixture was filtered and the solvent was evaporated under reduced pressure. The residue was dissolved in aqueous sodium hydroxide (1M) and the mixture was extracted with ethyl acetate. The combined organic fractions were washed with water, dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was dissolved in diethyl ether and ethereal hydrogen chloride (1M, 50 mL) was added. The solid was collected, washing with diethyl ether, and dried *in vacuo* to give the title compound as a colorless solid (6.82 g, 93%). m/z (ES^+) 135 (M+1-NH_3).

DESCRIPTION 7

(*RS*)-α-Ethyl-3,5-bis(trifluoromethyl)benzenemethanamine Hydrochloride

Prepared from 1-[3,5-bis(trifluoromethyl)phenyl]propanone according to the method of Description 6. m/z (ES^+) 272 (M+1), 255 (M+1-NH_3).

DESCRIPTION 8

Methyl 3,5-Bis(trifluoromethyl)benzeneacetate

Sulfuric acid (conc., 1 mL) was added to a solution of 3,5-bis(trifluoromethyl) benzeneacetic acid (50.0 g, 0.18 mol) in methanol (400 mL) and the mixture was stirred at room temperature for 1 week. The solvent was evaporated and ethyl acetate (100 mL) and aqueous sodium hydrogen carbonate (saturated, 600 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 300 mL). The combined organic fractions were washed with brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound (49.0 g, 93%). ^{1}H NMR (400MHz, $CDCl_3$) 7.80 (1H, s), 7.75 (2H, s), 3.77 (2H, s), and 3.75 (3H, s).

DESCRIPTION 9

Methyl α,α-Dimethyl-3,5-bis(trifluoromethyl)benzeneacetate

Sodium hydride (60 % in mineral oil, 2.1 g, 52.5 mmol) was added in portions to a solution of methyl 3,5-bis(trifluoromethyl)benzeneacetate (Description 8, 5 g, 17.5 mmol) in dimethylformamide (100 mL) and the mixture was stirred for 10 minutes. Iodomethane (5.45 mL, 87.5 mmol) was added and the mixture was stirred at room temperature overnight. Aqueous ammonium chloride (saturated) was added and the mixture was extracted with ethyl acetate. The combined organic fractions were washed with water, dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with isohexane/EtOAc (100:0 increasing to 90:10) to give the title compound as a colorless oil (5.34 g, 97%). ^1H NMR (400MHz, $CDCl_3$) δ 7.78 (3H, s), 3.69 (3H, s), and 1.65 (6H, s).

DESCRIPTION 10

α,α-Dimethyl-3,5-bis(trifluoromethyl)benzeneacetic Acid

Lithium hydroxide monohydrate (2.13 g, 50.6 mmol) was added to a suspension of methyl α,α-dimethyl-3,5-bis(trifluoromethyl)benzeneacetate (Description 9, 5.3 g, 16.88 mmol) in methanol (60 mL), water (20 mL) and tetrahydrofuran (20 mL) and the mixture was degassed and stirred at room temperature for 3 days. The solvent was evaporated under reduced pressure and the residue was suspended in hydrochloric acid (1M). The mixture was extracted with ethyl acetate and the combined organic fractions were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound as a colorless solid (5.05 g, 100%). ^1H NMR (400MHz, $CDCl_3$) δ 7.84 (2H, s), 7.80 (1H, s), and 1.68 (6H, s).

DESCRIPTION 11

α,α-Dimethyl-3,5-bis(trifluoromethyl)benzenemethanamine Hydrochloride

Diphenylphosphoryl azide (0.43 mL, 2 mmol) was added to asolution of α,α-dimethyl-3,5-bis(trifluoromethyl)benzeneacetic acid (Description 10, 0.5 g, 1.67 mmol) and triethylamine (0.6 mL, 4.2 mmol) in toluene (20 mL) and the mixture was stirred at 90 °C for 18 hours. The mixture was cooled, diluted with ethyl acetate and washed with aqueous sodium carbonate (saturated), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. Hydrochloric acid (5M, 15 mL) was added and the mixture was heated under reflux for 18 hours. The mixture was cooled, basified with aqueous sodium hydroxide (4M) and extracted with ethyl acetate. The combined organic fractions were washed with water, dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was dissolved in diethyl

ether and ethereal hydrogen chloride (1M) was added. The solid was collected, washing with diethyl ether, and dried *in vacuo* to give the title compound as a colorless solid (100 mg, 20%). m/z (ES^+) 272 (M+1), 255 (M+1-NH_3).

DESCRIPTION 12

(*RS*)-Methyl α-Amino-3,5-bis(trifluoromethyl)benzeneacetate Hydrochloride

Palladium on carbon (5%, 220 mg) was added to a solution of methyl α-diazo-3,5-bis(trifluoromethyl)benzeneacetate (WO 9521819, 1.22 g, 3.91 mmol) in methanol/acetic acid (3:1, 33 mL) and the mixture was shaken under an atmosphere of hydrogen (40 psi) for 18 hours. The mixture was filtered through a glass fibre pad and the solvent was evaporated under reduced pressure. Ethyl acetate (100 mL) and aqueous sodium carbonate (10%, 100 mL) were added and the layers were separated. The aqueous fraction was extracted with ethyl acetate (50 mL) and the combined organic fractions were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (30 mL) and ethereal hydrogen chloride (1M, 5 mL) was added. The solid was collected, washing with ethyl acetate and ether, and dried *in vacuo* to give the title compound (432 mg, 33%). m/z (ES^+) 302 (M+1).

DESCRIPTION 13

2-(Cyclopropyloxy)-5-(trifluoromethoxy)phenylmethyl Methanesulfonate

Methanesulfonyl chloride (0.31 mL, 0.46 g, 4.0 mmol) was added dropwise to a stirred, cooled (-10 °C) solution of 2-(cyclopropyloxy)-5-(trifluoromethoxy)benzenemethanol (WO9900368, 0.5 g, 2.0 mmol) and triethylamine (0.56 mL, 0.40 g, 4.0 mmol) in dichloromethane (10 mL) and the mixture was stirred at 0 °C for 30 minutes, then at room temperature for 2 hours. Water (50 mL) was added and the mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic fractions were washed with aqueous citric acid (10%, 20 mL), aqueous sodium hydrogen carbonate (saturated, 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound. ^1H NMR (400MHz, $CDCl_3$) δ 7.28-7.22 (3H, m), 5.20 (2H, s), 3.80-3.77 (1H, m), 3.01 (3H, s), and 0.85-0.79 (4H, m).

DESCRIPTION 14

4-(4-Fluorophenyl)pyridine

A mixture of 4-fluorobenzeneboronic acid (38.7 g, 276 mmol), 4-bromopyridine hydrochloride (48.9 g, 250 mmol), [1,4-butanediylbis(diphenylphosphine-κP)] dichloropalladium (*Organometallics* **1998**, *17*, 661; 1.52 g, 2.5 mmol), 1,2-dimethoxyethane

(500 mL) and sodium carbonate solution (2M, 440 mL) was degassed with bubbling nitrogen and stirred at 80 °C for 24 hours. The mixture was cooled and extracted with ethyl acetate. The combined organic fractions were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the crude title compound as a brown solid (50.87 g) which was used without further purification. ^{1}H NMR (360MHz, $CDCl_3$) δ 8.65 (2H, m), 7.61 (2H, m), 7.49 (2H, dd, *J* 1.6, 4.6 Hz), and 7.09 (2H, m).

DESCRIPTION 15

4-(4-Fluorophenyl)-1,2,3,6-tetrahydro-1-(phenylmethyl)pyridine

Benzyl bromide (52.4 mL, 441 mmol) was added to a solution of 4-(4-fluorophenyl)pyridine (Description 14, 50.87 g, 294 mmol) in acetone (500 mL) and the mixture was heated under reflux for 3 days. The mixture was cooled to room temperature and the solid was collected, washed with acetone and diethyl ether and dried *in vacuo*. The solid was dissolved in methanol (400 mL) and water (100 mL), cooled to 0 °C and sodium borohydride (20.6 g, 542 mmol) was added in portions. The mixture was stirred at room temperature for 1 hour, then heated to reflux for 18 hours. The mixture was cooled and the solvent was evaporated under reduced pressure. Dichloromethane (300 mL) and water (200 mL) were added and the layers were separated. The organic layer was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound as a light brown oil (61.5 g, 78%). m/z (ES^+) 268 (M+1).

DESCRIPTION 16

4-(4-Fluorophenyl)piperidine

Palladium hydroxide on carbon (20%, 5 g) was added to a solution of 4-(4-fluorophenyl)-1,2,3,6-tetrahydro-1-(phenylmethyl)pyridine (Description 15, 60 g, 225 mmol) in methanol (500 mL) and the mixture was shaken under an atmosphere of hydrogen (50 psi) for 48 hours. The mixture was filtered through a glass fibre pad, washing with methanol, and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and ethereal hydrogen chloride (1M, 300 mL) was added. The solid was collected and recrystallised from 2-propanol to give *4-(4-fluorophenyl)piperidine hydrochloride* as a colorless solid (30.5 g, 63%). ^{1}H NMR (400MHz, CD_3OD) δ 7.31-7.27 (2H, m), 7.09-7.03 (2H, m), 3.48 (2H, m), 3.30 (2H, td, *J* 3.0, 13.1 Hz), 2.91 (1H, m), 2.05 (2H, m), and 1.87 (2H, m). m/z (ES^+) 180 (M+1).

A sample (1 g, 4.64 mmol) was suspended in ethyl acetate and washed with saturated aqueous sodium carbonate. The organic layer was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound as a colorless oil (825 mg, 99%). ^{1}H NMR

(400MHz, CD_3OD) δ 7.25-7.21 (2H, m), 7.02-6.97 (2H, m), 3.14 (2H, m), 2.78-2.64 (3H, m), 1.80 (2H, m), and 1.63 (2H, m). m/z (ES^+) 180 (M+1).

DESCRIPTION 17

Benzenebutanal

1,1,1-Tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (1.7 g, 4.0 mmol) was added to a solution of benzenebutanol (0.5 g, 3.3 mmol) in dichloromethane (10 mL) and the mixture was stirred at room temperature for 2 hours. The mixture was filtered through a plug of silica gel, washing with dichloromethane, and the solvent was evaporated under reduced pressure to give the title compound as a colorless oil (466 mg, 95%). ^1H NMR (400MHz, $CDCl_3$) δ 9.76 (1H, m), 7.31-27 (2H, m), 7.22-7.16 (3H, m), 2.66 (2H, t, *J* 7.3 Hz), 2.45 (2H, t, *J* 7.3 Hz), 1.97 (2H, quin, *J* 7.3 Hz).

DESCRIPTION 18

Methyl 4-Oxo-1-phenylcyclohexanecarboxylate

Acetyl chloride (0.46 mL, 0.50 g, 6.4 mmol) was added to a solution of 4-oxo-1-phenylcyclohexanecarboxylic acid (Description 2, 0.94 g, 4.3 mmol) in methanol (5 mL) and the mixture was heated under reflux for 20 hours. The mixture was cooled, poured into aqueous sodium hydrogen carbonate (saturated, 100 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (2 mL), acetic acid (6 mL) and water (2 mL) were added and the mixture was stirred at 45 °C for 2 hours. The mixture was cooled, the solvent was evaporated under reduced pressure and aqueous sodium hydrogen carbonate (saturated, 100 mL) was added. The mixture was extracted with ethyl acetate (2 x 50 mL), the combined organic fractions were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give the title compound (0.98 g, 98%). ^1H NMR (250MHz, $CDCl_3$) δ 7.45-7.26 (5H, m), 3.72 (3H, s), 2.77 (2H, m), 2.61-2.38 (4H, m), and 2.25 (2H, m).

DESCRIPTION 19

Cis-Methyl 4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylate, *Cis*-4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylic Acid and *Trans*-Methyl 4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylate

A solution of sodium cyanoborohydride (0.93 g, 14.9 mmol) and zinc chloride (1.01 g, 7.45 mmol) in methanol (30 mL) was added to a solution of methyl 4-oxo-1-phenylcyclohexanecarboxylate (Description 18, 3.45 g, 14.9 mmol) and 4-(4-

fluorophenyl)piperidine (Description 16, 3.2 g, 17.9 mmol) in methanol (50 mL) and the mixture was stirred at room temperature for 24 hours. The mixture was poured into water and extracted with ethyl acetate and the combined organic fractions were dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was recrystallised from ethanol to give cis-*methyl 4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylate* (0.9 g, 15%) as a colorless solid. ^{1}H NMR (400MHz, CD_3OD) δ 7.38-7.36 (2H, m), 7.33-7.29 (2H, m), 7.26-7.20 (3H, m), 7.02-6.98 (2H, m), 3.66 (3H, s), 3.10 (2H, m), 2.71 (2H, m), 2.56-2.52 (1H, m), 2.43-2.32 (3H, m), 2.05 (2H, m), 1.84 (2H, m), 1.78-1.62 (4H, m), and 1.54-1.48 (2H, m). m/z (ES^+) 396 (M+1).

The mother liquors from the recrystallisation were collected and the solvent was evaporated under reduced pressure. Methanol (20 mL) and hydrochloric acid (6M, 200 mL) were added and the mixture was heated under reflux for 3 days. The mixture was cooled and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (100 mL) and acetyl chloride (0.77 mL, 10.8 mmol) was added slowly. The mixture was heated under reflux for 6 hours, cooled and the solvent was evaporated under reduced pressure. Ethyl acetate and aqueous sodium carbonate (saturated) were added and the layers were separated. The solid which formed in the organic layer was collected and dried *in vacuo* to give cis-*methyl 4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylic acid* as a colorless solid (1.2 g, 21%). m/z (ES^+) 382 (M+1).

The mother liquors from the recrystallisation were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give trans-*methyl 4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylate* as a colorless solid, (1.6 g, 27%).
^{1}H NMR (400MHz, CD_3OD) δ 7.51-7.48 (2H, m), 7.38-7.34 (2H, m), 7.24-7.17 (3H, m), 6.98-6.94 (2H, m), 3.56 (3H, s), 3.00 (2H, m), 2.79 (2H, m), 2.48-2.41 (2H, m), 2.24-2.17 (2H, m), 1.96-1.86 (4H, m), 1.75 (2H, m), 1.70-1.63 (2H, m), and 1.43-1.37 (2H, m). m/z (ES^+) 396 (M+1).

DESCRIPTION 20

Trans-4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylic Acid Hydrochloride

Hydrochloric acid (6M, 100 mL) was added to a suspension of *trans*-methyl 4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylate (Description 19, 1.6 g, 4.05 mmol) in methanol (10 mL) and the mixture was heated under reflux for 48 hours. The mixture was cooled and the solvent was evaporated under reduced pressure to give the title compound as a colorless solid (1.5 g, 89%). m/z (ES^+) 382 (M+1).

DESCRIPTION 21

Trans-4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanemethanol

Diisobutylaluminium hydride (1M in hexanes, 1.95 mL, 1.95 mmol) was added slowly to a cooled (-78 °C) solution of *trans*-methyl 4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylate (Description 19, 235 mg, 0.59 mmol) in dichloromethane (10 mL) and hexane (10 mL). The mixture was allowed to warm to room temperature and stirred for 18 hours. The mixture was poured into aqueous ammonium chloride (saturated) and extracted with dichloromethane. The combined organic fractions were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound as a pale yellow foam (230 mg, 100%). m/z (ES^+) 368 (m+1).

DESCRIPTION 22

(*RS*)-α-Methyl-8-phenyl-1,4-dioxaspiro[4.5]decane-8-methanol

A solution of 8-phenyl-1,4-dioxaspiro[4.5]decane-8-carboxaldehyde (*J.Med.Chem.* **1975**, *18*, 593-599; 4 g, 16.2 mmol) in tetrahydrofuran (100 mL) was added dropwise to a solution of methyl magnesium bromide (3.0M in ether, 8.1 mL, 24.3 mmol) in tetrahydrofuran (50 mL) at 0 °C. The mixture was allowed to warm to room temperature over 4 hours, then aqueous ammonium chloride (saturated, 75 mL), water (75 mL) and ethyl acetate (100 mL) were added. The layers were separated and the organic fraction was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound as a colorless solid (4.03 g, 96%). ^{1}H NMR (360MHz, $CDCl_3$) δ 0.96 (3H, d, *J* 6.5 Hz), 1.12 (1H, br s), 1.40-1.66 (4H, m), 1.76-1.86 (2H, m), 2.24-2.28 (1H, m), 2.46-2.51 (1H, m), 3.61-3.64 (1H, m), 3.85-3.96 (4H, m), and 7.21-7.38 (5H, m).

DESCRIPTION 23

(*RS*)-α-Ethenyl-8-phenyl-1,4-dioxaspiro[4.5]decane-8-methanol

Prepared from 8-phenyl-1,4-dioxaspiro[4.5]decane-8-carboxaldehyde (*J.Med.Chem.* **1975**, *18*, 593-599) and vinylmagnesium bromide according to the method of Description 22. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.31 (1H, br s), 1.42-1.69 (4H, m), 1.76-1.89 (2H, m), 2.23-2.28 (1H, m), 2.45-2.51 (1H, m), 3.85-3.96 (5H, m), 5.09-5.14 (2H, m), 5.55-5.63 (1H, m), and 7.21-7.39 (5H, m).

DESCRIPTION 24

Trans-4-(4-Oxopiperidin-1-yl)-1-phenylcyclohexanecarboxylic Acid Hydrochloride

Sodium acetoxyborohydride (7.0 g, 32.9 mmol) was added to a degassed solution of 4-oxo-1-phenylcyclohexanecarboxylic acid (Description 2, 5.98 g, 27.4 mmol) and 1,4-dioxa-8-azaspiro[4.5]decane (4.32 g, 30.2 mmol) in dichloroethane (125 mL) and the mixture was stirred at room temperature for 20 hours. The solvent was evaporated under reduced pressure, methanol (120 mL) was added and the mixture was stirred at room temperature for 1 hour. The mixture was filtered and cooled to 0 °C. Acetyl chloride (10 mL) was added slowly and the mixture was heated under reflux for 20 hours. The mixture was cooled, filtered and the solvent was evaporated under reduced pressure. Aqueous sodium carbonate (saturated, 200 mL) was added and the mixture was extracted with ethyl acetate (2 x 200 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. Hydrochloric acid (5M, 300 mL) was added and the mixture was heated under reflux for 20 hours. The mixture was cooled and the solvent was evaporated under reduced pressure to give the title compound (3.36 g, 36%). m/z (ES^+) 302 (M+1).

DESCRIPTION 25

Trans-4-[4-(Phenylmethyl)piperazin-1-yl]-1-phenylcyclohexanecarboxylic Acid Hydrochloride

Prepared from 4-oxo-1-phenylcyclohexanecarboxylic acid (Description 2) and 1-(phenylmethyl) piperazine according to the method of Description 24. m/z (ES^+) 379 (M+1).

DESCRIPTION 26

Cis-(*RS*)-4-Hydroxy-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyllethyl} cyclohexanecarboxamide

Sodium borohydride (0.31 g, 8.3 mmol) in ethanol (10 mL) was added dropwise over 10 minutes to a stirred, cooled (0 °C) solution of (*RS*)-4-oxo-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide (Example 18, 1.90 g, 4.1 mmol) in ethanol (60 mL). The mixture was stirred at 0 °C for 30 minutes, then hydrochloric acid (2M, 20 mL) was added. The mixture was stirred at room temperature for 10 minutes, then the pH was adjusted to 7.0 with aqueous potassium carbonate (saturated) and the ethanol was evaporated under reduced pressure. Water (50 mL) was added and the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic fractions were washed with aqueous sodium hydrogen carbonate (saturated, 2 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was crystallized from EtOH/H_2O (50:50, 30 mL) and the solid was collected and dried *in vacuo* at 40 °C to give the title

compound (1.37 g, 72%). ^{1}H NMR (400MHz, CD_3OD) δ 7.76 (1H, s), 7.69 (2H, s), 7.32-7.17 (5H, m), 5.16 (1H, q, *J* 7.1 Hz), 3.60 (1H, m), 2.62 (2H, m), 1.97-1.47 (6H, m), and 1.43 (3H, d, *J* 7.1 Hz).

DESCRIPTION 27

Cis-(*RS*)-4-Methanesulfonyloxy-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide

Methanesulfonyl chloride (0.9 mL, 11.6 mmol) was added to a stirred, cooled (0 °C) solution of *cis*-(*RS*)-4-hydroxy-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl} cyclohexanecarboxamide (Description 26, 1.33 g, 2.9 mmol) and pyridine (0.94 mL, 11.6 mmol) in dichloromethane (100 mL) and the mixture was stirred at room temperature for 24 hours. The mixture was washed with aqueous citric acid (10%) and aqueous sodium hydroxide (1M), dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure to give the title compound as a colorless foam (1.44 g, 95%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.72 (1H, s), 7.44 (2H, s), 7.42-7.38 (2H, m), 7.35-7.31 (3H, m), 5.41 (1H, d, *J* 6.9 Hz), 5.07 (1H, m), 4.78 (1H, m), 3.03 (3H, s), 2.60-2.40 (2H, m), 2.14-1.87 (6H, m), and 1.35 (3H, d, *J* 7.0 Hz).

DESCRIPTION 28

Trans-(*RS*)-4-Azido-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide

Sodium azide (621 mg, 9.55 mmol) was added to a solution of *cis*-(*RS*)-4-methanesulfonyloxy-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide (Description 27, 1.0 g, 1.91 mmol) in dimethylformamide (15 mL) and the mixture was then stirred at 90 °C for 24 hours. The mixture was cooled, poured into aqueous ammonium chloride (saturated) and extracted with ethyl acetate. The combined organic fractions were washed with aqueous ammonium chloride (saturated) and water, dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure to give the title compound as a yellow solid (920 mg, 100%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.72 (1H, s), 7.45-7.31 (7H, m), 5.34 (1H, d, *J* 7.0 Hz), 5.03 (1H, m), 3.63 (1H, m), 2.41-2.37 (1H, m), 2.23-2.12 (3H, m), 1.99-1.93 (2H, m), 1.67-1.47 (2H, m), and 1.30 (3H, d, *J* 7.0 Hz).

DESCRIPTION 29

Trans-(*RS*)-4-Cyano-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide

Tetrabutylammonium cyanide (153 mg, 0.57 mmol) was dried azeotropically by evaporating toluene under reduced pressure, then a solution of *cis*-(*RS*)-4-methanesulfonyloxy-N-{1-[3,5-bis(trifluoromethyl) phenyl]ethyl}-1-phenylcyclohexanecarboxamide (Description 27, 100 mg, 0.19 mmol) in toluene (10 mL) was added and the mixture was stirred at 70 °C for 9 hours. Further tetrabutylammonium cyanide (153 mg, 0.57 mmol) was added and the mixture was stirred at 70 °C for 24 hours. The mixture was poured into water (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic fractions were washed with water (50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with isohexane/EtOAc (80:20), to give the title compound (50 mg, 56%). ^{1}H NMR (360MHz, CD_3OD) δ 7.76 (1H, s), 7.66 (2H, s), 7.36-7.22 (5H, m), 5.12 (1H, q, *J* 7.0 Hz), 3.00-2.96 (1H, m), 2.48-2.39 (2H, m), 2.29-2.21 (1H, m), 2.04-1.79 (5H, m), and 1.41 (3H, d, *J* 7.0 Hz).

DESCRIPTION 30

Cis- and *Trans*-4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarbonitrile

Prepared as a mixture of *cis*- and *trans*-isomers from 4-oxo-1-phenylcyclohexanecarbonitrile and 4-(4-fluorophenyl)piperidine (Description 16) according to the method of Example 55. m/z (ES^+) 363 (M+1).

DESCRIPTION 31

Trans-4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarbonitrile

Prepared from the mixture of isomers of Description 30 by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_3(Aq.) (98:2:0.2). m/z (ES^+) 363 (M+1).

DESCRIPTION 32

Trans-4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanemethanamine

Lithium aluminium hydride (1M in ether, 0.69 mL, 0.69 mmol) was added to a solution of *trans*-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarbonitrile (Description 31, 250 mg, 0.69 mmol) in ether (10 mL) and the mixture was stirred at room temperature for 1 hour. Water (0.5 mL), aqueous sodium hydroxide (1M, 1 mL) and water (1.5 mL) were added and the mixture was stirred at room temperature for 10 minutes. The mixture was filtered, washing with ether, and the layers were separated. The organic layer was washed

with brine (10 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound (243 mg, 96%). m/z (ES^+) 367 (M+1).

DESCRIPTION 33

2-({(2-[3,5-Bis(trifluoromethyl)phenyl]ethyl}thio)benzothiazole

Tributylphosphine (3.46 mL, 2.81 g, 13.9 mmol) was added over 30 minutes to a mixture of 3,5-bis(trifluoromethyl)benzeneethanol (3.26 g, 12.6 mmol) and 2,2'-dithiobis(benzothiazole) (4.20 g, 12.6 mmol) in tetrahydrofuran (120 mL) and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure and water (150 mL) was added. The mixture was extracted with ether (2 x 150 mL) and the combined organic fractions were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with isohexane/EtOAc (90:10) to give the title compound (3.87 g, 75%). m/z (ES^+) 408 (M+1).

DESCRIPTION 34

2-({(2-[3,5-Bis(trifluoromethyl)phenyl]ethyl}sulfonyl)benzothiazole

Oxone (8.58 g, 14.0 mmol) was added to a mixture of 2-({(2-[3,5-bis(trifluoromethyl)phenyl]ethyl}thio)benzothiazole (Description 33, 2.47 g, 6.1 mmol) and wet alumina (7 g) in chloroform (100 mL) and the mixture was heated under reflux for 1 hour. The mixture was cooled, filtered and the solvent was evaporated under reduced pressure to give the title compound (2.62 g, 99%). m/z (ES^+) 440 (M+1).

DESCRIPTION 35

(*E*)-8-Phenyl-8-{3-[3,5-bis(trifluoromethyl)phenyl]prop-1-enyl}-1,4-dioxaspiro[4.5]decane

Lithium hexamethyldisilazide (1M in tetrahydrofuran, 7.0 mL, 7.0 mmol) was added over 10 minutes to a cooled (-78 °C) solution of 8-phenyl-1,4-dioxaspiro[4.5]decane-8-carboxaldehyde (*J.Med.Chem.* **1975**, *18*, 593-599, 1.68 g, 6.8 mmol) and 2-({(2-[3,5-bis(trifluoromethyl)phenyl]ethyl}sulfonyl)benzothiazole (Description 34, 2.99 g, 6.8 mmol) in tetrahydrofuran (15 mL) and the mixture was stirred at -78 °C for 1 hour, then allowed to warm to room temperature. Aqueous ammonium chloride (saturated, 10 mL) was added and the mixture was stirred at room temperature for 30 minutes. Water (5 mL) was added and the mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic fractions were washed with brine (50 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with isohexane/EtOAc (90:10) to give the title compound as a pale yellow oil (2.43 g, 92%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.70 (1H, s), 7.56 (2H, s), 7.36-7.18 (5H, m), 5.65 (1H, d, *J*

15.3 Hz), 5.41 (1H, dt, J_d 15.3, J_t 7.0 Hz), 3.94 (4H, m), 3.45 (2H, d, *J* 7.0 Hz), 2.22 (2H, m), 1.99 (2H, m), and 1.75-1.61 (4H, m).

DESCRIPTION 36

Trans-(*RS*)-4-Methyl-3-piperidinol Hydrochloride

A slurry of palladium on carbon (10%, 600 mg) in ethanol (10 mL) was added to a solution of *trans*-(*RS*)-4-methyl-1-(phenylmethyl)-3-piperidinol (*Tetrahedron* **1970**, *26*, 5519-5527, 6 g, 29.2 mmol) and hydrochloric acid (2M, 10 mL) in ethanol (100 mL) and the mixture was shaken under hydrogen (50 psi) for 42 hours. The mixture was filtered through Celite™ and the solvent was evaporated under reduced pressure. Toluene (50 mL) was added and evaporated under reduced pressure to give the title compound as a colorless solid (4.4 g, 99%). m/z (ES^+) 115 (M+1).

DESCRIPTION 37

Trans-(*RS*)-1,1-Dimethylethyl 3-Hydroxy-4-methylpiperidinecarboxylate

Di-tert-butyl dicarbonate (4.32 g, 20 mmol) was added to a solution of *trans*-(*RS*)-4-methyl-3-piperidinol hydrochloride (Description 36, 2.93 g, 19.4 mmol) and triethylamine (4.1 mL, 29 mmol) in dichloromethane (150 mL) and the mixture was stirred at room temperature for 16 hours. N,N-Dimethylethylenediamine (506 µL) was added and the mixture was stirred at room temperature for 16 hours. The mixture was washed with aqueous citric acid (10%, 100 mL), dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give the title compound as a colorless oil (4.0 g, 96%). m/z (ES^+) 159 (M+1).

DESCRIPTION 38

(*RS*)-1,1-Dimethylethyl 4-Methyl-3-oxopiperidinecarboxylate

1,1,1-Tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (4.17 g, 0.13 mmol) was added to a solution of *trans*-(*RS*)-1,1-dimethylethyl 3-hydroxy-4-methylpiperidinecarboxylate (Description 37, 2 g, 9.3 mmol) in dichloromethane (60 mL) and the mixture was stirred at room temperature for 60 minutes. Aqueous sodium bisulfite (10%, 50 mL) was added) and the mixture was stirred at room temperature for 5 minutes. Saturated aqueous sodium hydrogen carbonate (50 mL) was added and the layers were separated. The organic fraction was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound (1.96 g, 99%). m/z (ES^+) 157 (M+1).

DESCRIPTION 39

(*RS*)-3,3-Difluoro-4-methylpiperidine Hydrochloride

Diethylaminosulphur trifluoride (1.18 mL, 8.97 mmol) was added to a stirred, cooled (0 °C) solution of (*RS*)-1,1-dimethylethyl 4-methyl-3-oxopiperidinecarboxylate (Description 38, 500 mg, 2.24 mmol) in dichloromethane and the mixture was stirred at room temperature for 16 hours. Ice (5 g) and water (5 mL) were added and the mixture was stirred at room temperature for 20 minutes. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 50 mL). The combined organic fractions were washed with brine (50 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was suspended in diethyl ether (50 mL) and treated with methanolic hydrogen chloride (1M, 3 mL). The mixture was stirred at room temperature for 30 minutes, then the solvent was evaporated under reduced pressure to give the title compound as a solid (303 mg, 78%). m/z (ES^+) 136 (M+1).

DESCRIPTION 40

1-(1,1-Dimethylethyl) 4-Ethyl 4-(2-Propenyl)-1,4-piperidinedicarboxylate

A solution of 1-(1,1-dimethylethyl) 4-ethyl 1,4-piperidinedicarboxylate (25.0 g, 97 mmol) in tetrahydrofuran (100 mL) was added slowly to a stirred, cooled (-78 °C) solution of potassium hexamethyldisilazide (29.0 g, 145 mmol) in tetrahydrofuran (150 mL), maintaining the internal temperature below -65 °C. The mixture was stirred at -78 °C for 30 minutes, then 3-bromopropene (12.6 mL, 145 mmol) was added dropwise over 10 minutes. The mixture was stirred at -78 °C for 1 hour, then saturated aqueous ammonium chloride (400 mL) and water (100 mL) were added and the mixture was warmed to room temperature. The mixture was extracted with ethyl acetate (3 x 400 mL) and the combined organic fractions were washed with aqueous citric acid (10%, 2 x 250 mL), saturated aqueous sodium hydrogen carbonate (400 mL) and brine (200 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound (29.3 g, 100%). ^1H NMR (400MHz, $CDCl_3$) δ 5.75-5.60 (1H, m), 5.10-5.00 (2H, m), 4.16 (2H, q, *J* 7 Hz), 3.92-3.78 (2H, m), 2.90 (2H, br t, *J* 14 Hz), 2.26 (2H, d, *J* 7 Hz), 2.08 (2H, br d, *J* 14 Hz), 1.45 (9H, s), 1.45-1.30 (2H, m), and 1.26 (3H, t, *J* 7 Hz).

DESCRIPTION 41

1,1-Dimethylethyl 1-Oxo-2-oxa-8-azaspiro[4.5]decane-8-carboxylate

1-(1,1-Dimethylethyl) 4-ethyl 4-(2-propenyl)-1,4-piperidinedicarboxylate (Description 40, 20.0 g, 67.2 mmol) was dissolved in methanol (300 mL) and dichloromethane (300 mL) and cooled to -78 °C. Oxygen was bubbled through the solution for 10 minutes, then ozone for

75 minutes, to give a persistant blue coloration. Oxygen was bubbled through the solution for 10 minutes, then nitrogen for 10 minutes. Sodium borohydride (5.1 g, 135 mmol) was added and the mixture was stirred at -78 °C for 1 hour. Further sodium borohydride (5.1 g, 135 mmol) was added and the mixture was stirred at room temperature for 16 hours. Acetone (75 mL) was added and the mixture was stirred at room temperature for 10 minutes. Water (50 mL) was added and the organic solvent was evaporated under reduced pressure. Saturated aqueous ammonium chloride (500 mL) was added and the mixture was extracted with ethyl acetate (2 x 500 mL). The combined organic fractions were washed with aqueous citric acid (10%, 500 mL), saturated aqueous sodium hydrogen carbonate (500 mL) and brine (200 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give the title compound (15.0 g, 88%). ^{1}H NMR (400MHz, $CDCl_3$) δ 4.31 (2H, t, *J* 7 Hz), 3.97-3.87 (2H, m), 3.17-3.07 (2H, m), 2.20 (2H, t, *J* 7 Hz), 1.92-1.82 (2H, m), 1.60-1.45 (2H, m), and 1.45 (9H, s).

DESCRIPTION 42

1,1-Dimethylethyl 4-(2-Hydroxyethyl)-4-(hydroxymethyl)-1-piperidinecarboxylate

Diisobutylaluminium hydride (1.0M in dichloromethane, 3.60 mL, 3.60 mmol) was added over 10 minutes to a stirred, cooled (-78 °C) solution of 1,1-dimethylethyl 1-oxo-2-oxa-8-azaspiro[4.5]decane-8-carboxylate (Description 41, 400 mg, 1.57 mmol) in dichloromethane (4 mL) and the mixture stirred at -78 °C for 3 hours, then at 0 °C for 2 hours. Water (1.6 mL) was added very slowly at 0 °C and the mixture was warmed to room temperature and stirred overnight. The mixture was filtered through Hyflo™, washing with dichloromethane, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with ethyl acetate, to give the title compound (255 mg, 63%). m/z (ES^+) 260 (M+1).

DESCRIPTION 43

1,1-Dimethylethyl 2-Oxa-8-azaspiro[4.5]decane-8-carboxylate

Diethyl azodicarboxylate (183 µl, 1.16 mmol) in tetrahydrofuran (0.5 mL) was added dropwise to a stirred, cooled (0 °C) solution of 1,1-dimethylethyl 4-(2-hydroxyethyl)-4-(hydroxymethyl)-1-piperidinecarboxylate (Description 42, 250 mg, 0.96 mmol) and triphenylphosphine (303 mg, 1.16 mmol) in tetrahydrofuran (10 mL) and the mixture was stirred at 0 °C for 90 minutes then at room temperature overnight. The mixture was cooled to 0 °C and further triphenylphosphine (126 mg, 0.48 mmol) and diethyl azodicarboxylate (76 µl, 0.48 mmol) were added. The mixture was stirred at room temperature for 2.5 hours, then the solvent was evaporated under reduced pressure and the residue was purified by flash

column chromatography on silica gel, eluting with isohexane/EtOAc (80:20), to give the title compound as a colorless oil (150 mg, 65%). m/z (ES^+) 186 (M+1-C_4H_8).

DESCRIPTION 44

2-Oxa-8-azaspiro[4.5]decane

Methanolic hydrogen chloride (3M, 3 mL) was added to a stirred, cooled (0 °C) solution of 1,1-dimethylethyl 2-oxa-8-azaspiro[4.5]decane-8-carboxylate (Description 43, 150 mg, 0.62 mmol) in methanol and the mixture was stirred at room temperature for 24 hours. The solvent was evaporated under reduced pressure and the residue was dissolved in methanol and passed through Amberlyst 26 ion exchange resin, eluting with methanol. The solvent was evaporated under reduced pressure and the residue was dissolved in dichloromethane, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give the title compound (77 mg, 88%). m/z (ES^+) 142 (M+1).

EXAMPLE 1

1-{[(1,4-Dioxa-8-phenylspiro[4.5]decan-8-yl)methoxy]methyl}-2-methoxybenzene

Sodium hydride (60% dispersion in mineral oil, 720 mg, 30.0 mmol) was added to a solution of 8-phenyl-1,4-dioxaspiro[4.5]decane-8-methanol (*J. Org.Chem.* **1974**, *39*, 2311-2313, 1.5 g, 6.0 mmol) in dimethylformamide (20 mL) and the mixture was stirred at room temperature for 1 hour. 1-(Chloromethyl)-2-methoxybenzene (816 mg, 6.0 mmol) was added and the mixture was stirred overnight at 50 °C. The mixture was cooled, poured into water (50 mL) and extracted with ether (2 x 50 mL). The combined organic fractions were washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with isohexane/EtOAc (90:10), to give the title compound as a colorless solid (930 mg, 42%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.43-7.40 (2H, m), 7.33-7.29 (2H, m), 7.21-7.13 (3H, m), 6.86 (1H, td, *J* 0.6, 7.4 Hz), 6.78 (1H, d, *J* 8.2 Hz), 4.41 (2H, s), 3.95-3.86 (4H, m), 3.74 (3H, m), 3.41 (2H, s), 2.26 (2H, dd, *J* 3.2, 15.0 Hz), 1.98 (2H, dd, *J* 3.6, 13.0 Hz), and 1.68-1.53 (4H, m).

EXAMPLE 2

1-({[4-Oxo-1-phenylcyclohexyl]methoxy}methyl)-2-methoxybenzene

Prepared from 1-{[(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)methoxy]methyl}-2-methoxybenzene (Example 1) according to the method of Example 10. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.50-7.47 (2H, m), 7.41-7.37 (2H, m), 7.30-7.15 (3H, m), 6.89 (1H, td, *J* 0.7,

7.4 Hz), 6.81 (1H, d, *J* 8.2 Hz), 4.44 (2H, s), 3.76 (3H, s), 3.46 (2H, s), 2.56-2.51 (2H, m), and 2.34-2.17 (6H, m).

EXAMPLE 3

1-{[(1,4-Dioxa-8-phenylspiro[4.5]decan-8-yl)methoxy]methyl}-2-(cyclopropoxy)-5-(trifluoromethoxy)benzene

Prepared from 8-phenyl-1,4-dioxaspiro[4.5]decane-8-methanol (*J. Org. Chem.* **1974**, *39*, 2311-2313) and 2-(cyclopropyloxy)-5-(trifluoromethoxy)phenylmethyl methanesulfonate (Description 13) according to the method of Example 1. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.42 (2H, dd, *J* 8.0, 1.0 Hz), 7.32 (2H, t, *J* 8.0 Hz), 7.23-7.18 (1H, m), 7.12-7.09 (1H, m), 7.03-7.01 (2H, m), 4.31 (2H, s), 3.97-3.88 (4H, m), 3.68-3.63 (1H, m), 3.40 (2H, s), 2.29 (2H, d, *J* 14.0 Hz), 1.94 (2H, dt, J_d 4.0, J_t 14.0 Hz), 1.67-1.53 (4H, m), and 0.77-0.66 (4H, m).

EXAMPLE 4

1-({[4-Oxo-1-phenylcyclohexyl]methoxy}methyl)-2-(cyclopropoxy)-5-(trifluoromethoxy)benzene

Prepared from 1-{[(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)methoxy]methyl}-2-(cyclopropoxy)-5-(trifluoromethoxy)benzene (Example 3) according to the method of Example 10. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.49 (2H, d, *J* 7.6 Hz), 7.41 (2H, t, *J* 7.6 Hz), 7.29 (1H, t, *J* 7.6 Hz), 7.13 (1H, d, *J* 8.8 Hz), 7.06-7.00 (2H, m), 4.34 (2H, s), 3.69-3.65 (1H, m), 3.45 (2H, s), 2.61-2.56 (2H, m), 2.38-2.32 (4H, m), 2.17-2.09 (2H, m), and 0.79-0.66 (4H, m).

EXAMPLE 5

(*RS*)-1-[(α-Methyl-8-phenyl-1,4-dioxaspiro[4.5]decane-8-methoxy)methyl]-3,5-bis(trifluoromethyl)benzene

Sodium hydride (60% suspension in mineral oil, 700 mg, 30 mmol) was added in portions to a solution of (*RS*)-α-methyl-8-phenyl-1,4-dioxaspiro[4.5]decane-8-methanol (Description 22, 4 g, 15.3 mmol) in dimethylformamide (30 mL) and the mixture was stirred at room temperature for 1 hour. 1-(Bromomethyl)-3,5-bis(trifluoromethyl)benzene (2.8 mL, 15.3 mmol) was added and the mixture was stirred at 95 °C for 2.5 hours. The mixture was cooled, poured into water (500 mL) and extracted with diethyl ether (2 x 500 mL). The combined organic fractions were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with isohexane/EtOAc (90:10) to give the title compound as a pale oil (4.1 g, 55%). ^{1}H NMR (360MHz, $CDCl_3$) δ 0.98 (3H, d, *J* 6.5 Hz), 1.48-1.65 (4H, m), 1.87-1.97 (2H, m),

2.24-2.28 (1H, m), 2.43-2.50 (1H, m), 3.43 (1H, q, *J* 6.1 Hz), 3.86-3.96 (4H, m), 4.33 (1H, d, *J* 12.6 Hz), 4.61 (1H, d, *J* 12.6 Hz), 7.19-7.41 (5H, m), 7.69 (2H, s), and 7.75 (1H, s).

EXAMPLE 6

(*RS*)-1-[(α-Methyl-4-oxo-1-phenylcyclohexanemethoxy)methyl]-3,5-bis(trifluoromethyl)benzene

Prepared from (*RS*)-1-[(α-methyl-8-phenyl-1,4-dioxaspiro[4.5]decane-8-methoxy)methyl]-3,5-bis(trifluoromethyl)benzene (Example 5) according to the method of Example 10. ^{1}H NMR (360MHz, $CDCl_3$) δ 1.03 (3H, d, *J* 6.5 Hz), 1.98-2.15 (2H, m), 2.23-2.33 (4H, m), 2.53-2.58 (1H, m), 2.70-2.78 (1H, m), 3.50 (1H, q, *J* 6.1 Hz), 4.34 (1H, d, *J* 12.6 Hz), 4.63 (1H, d, *J* 12.6 Hz), 7.28-7.49 (5H, m), 7.67 (2H, s), and 7.77 (1H, s).

EXAMPLE 7

(*RS*)-1-[(α-Ethenyl-8-phenyl-1,4-dioxaspiro[4.5]decane-8-methoxy)methyl]-3,5-bis(trifluoromethyl)benzene

Prepared from (*RS*)-α-ethenyl-8-phenyl-1,4-dioxaspiro[4.5]decane-8-methanol (Description 23) and 1-(bromomethyl)-3,5-bis(trifluoromethyl)benzene according to the method of Example 5. ^{1}H NMR (360MHz, $CDCl_3$) δ 1.46-1.62 (4H, m), 1.76-1.90 (2H, m), 2.26-2.32 (1H, m), 2.45-2.54 (1H, m), 3.58 (1H, d, *J* 8.3 Hz), 3.85-3.95 (4H, m), 4.24 (1H, d, *J* 12.6 Hz), 4.53 (1H, d, *J* 12.6 Hz), 5.12-5.29 (2H, m), 5.40-5.50 (1H, m), 7.20-7.40 (5H, m), 7.61 (2H, s), and 7.73 (1H, s).

EXAMPLE 8

(*RS*)-1-[(α-Ethenyl-4-oxo-1-phenylcyclohexanemethoxy)methyl]-3,5-bis(trifluoromethyl)benzene

Prepared from (*RS*)-1-[(α-ethenyl-8-phenyl-1,4-dioxaspiro[4.5]decane-8-methoxy)methyl]-3,5-bis(trifluoromethyl)benzene (Example 7) according to the method of Example 10. ^{1}H NMR (360MHz, $CDCl_3$) δ 1.92-2.04 (2H, m), 2.22-2.41 (4H, m), 2.58-2.65 (1H, m), 2.77-2.83 (1H, m), 3.63 (1H, d, *J* 8.4 Hz), 4.26 (2H, d, *J* 12.8 Hz), 4.56 (1H, d, *J* 12.8 Hz), 5.17 (1H, d, *J* 17.2 Hz), 5.29-5.34 (1H, m), 5.45-5.54 (1H, m), 7.29-7.49 (5H, m), 7.59 (2H, s), and 7.75 (1H, s).

EXAMPLE 9

(1,4-Dioxa-8-phenylspiro[4.5]decan-8-yl)methyl 3,5-Bis(trifluoromethyl)benzoate

3,5-Bis(trifluoromethyl)benzoyl chloride (115 µl, 0.64 mmol) was added to a solution of 8-phenyl-1,4-dioxaspiro[4.5]decane-8-methanol (*J. Org.Chem.* **1974**, *39*, 2311-2313, 150 mg, 0.6 mmol) in dichloromethane (3 mL) and the mixture was stirred at room temperature for 16 hours. Triethylamine (83 µl, 0.6 mmol) and 4-dimethylamino pyridine (1 crystal) were added and the mixture was stirred at room temperature for 1 hour. 3,5-Bis(trifluoromethyl)benzoyl chloride (57 µl, 0.32 mmol) was added and the mixture was stirred at room temperature for 1 hour. The mixture was diluted with water (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic fractions were washed with brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel , eluting with isohexane/EtOAc (5:1), to give the title compound as a colorless oil (231 mg, 78%) contaminated with about 10% of (4-oxo-1-phenylcyclohexyl}methyl 3,5-bis(trifluoromethyl)benzoate. ^{1}H NMR (360MHz, $CDCl_3$) δ 1.55-1.73 (5H, m), 1.97 (2H, dt, *J* 3.7, 13.7 Hz), 2.39 (2H, m), 3.89-3.98 (4H, m), 7.23-7.27 (1H, m), 7.35-7.7.39 (2H, m), 7.45-7.47 (2H, m), 8.02 (1H, s), and 8.31 (2H, s).

EXAMPLE 10

(4-Oxo-1-phenylcyclohexyl}methyl 3,5-Bis(trifluoromethyl)benzoate

Hydrochloric acid (2M, 2 mL, 4 mmol) was added to a solution of (1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)methyl 3,5-bis(trifluoromethyl)benzoate (Example 9, 220 mg, 0.45 mmol) in acetone and the mixture was heated under reflux for 30 minutes. The mixture was cooled and the solvent was evaporated under reduced pressure. Aqueous sodium carbonate (saturated) was added and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were washed with brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound as a colorless solid (190 mg, 95%). ^{1}H NMR (360MHz, $CDCl_3$) δ 2.04-2.13 (2H, m), 2.37-2.42 (4H, m), 2.66-2.76 (2H, m), 4.37 (2H, s), 7.34 (1H, t, *J* 7.3 Hz), 7.46 (2H, t, *J* 7.7 Hz), 7.53-7.56 (2H, m), 8.04 (1H, s), and 8.32 (2H, s).

EXAMPLE 11

1-{1-[(1,4-Dioxa-8-phenylspiro[4.5]decan-8-yl)methoxy]ethenyl}-3,5-bis(trifluoromethyl)benzene

A solution of (1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)methyl 3,5-bis(trifluoromethyl)benzoate (Example 9, 500 mg, 1.0 mmol) in toluene (10 mL) was

degassed with a stream of nitrogen for 15 minutes. Dimethyltitanocene (0.2M in toluene, 10 mL, 2 mmol) was added and the mixture was degassed for a further 10 minutes. The mixture was heated at 90 °C in the dark for 12 hours, cooled, degassed for 10 minutes, and further dimethyltitanocene (0.2M in toluene, 5 mL, 1 mmol) was added. The mixture was heated at 90 °C in the dark for 15 hours, cooled, and sodium bicarbonate (3.1 g), methanol (50 mL) and water (1.9 mL) were added. The mixture was stirred at 40 °C for 2 hours, cooled, filtered through a bed of Celite™ and the solvent was evaporated under reduced pressure. The residue was diluted with water and extracted with ethyl acetate (2 x 50 mL). The combined organic fractions were washed with brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/isohexane (50:50), to give the title compound as a colorless gum (272 mg, 55%). ^{1}H NMR (360MHz, $CDCl_3$) δ 1.59-1.72 (4H, m), 1.96-2.04 (2H, m), 2.41(2H, br s, *J* 13.7 Hz), 3.77 (2H, s), 3.89-3.98 (4H, m), 4.27 (1H, d, *J* 3.3 Hz), 4.69 (1H, d, *J* 3.3 Hz), 7.23-7.27 (1H, m), 7.36-7.40 (2H, m), 7.47-7.50 (2H, m), 7.75 (1H, s), and 7.85 (2H, s).

EXAMPLE 12

(*RS*)-1-{1-[(1,4-Dioxa-8-phenylspiro[4.5]decan-8-yl)methoxy]ethyl]}-3,5-bis(trifluoromethyl)benzene

Palladium on carbon (5%, 20 mg) was carefully added as an aqueous slurry to a solution of 1-{1-[(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)methoxy]ethenyl]}-3,5-bis(trifluoromethyl)benzene (Description34, 265 mg, 0.5 mmol) in ethanol (20 mL) and ethyl acetate (2 mL) and the mixture was shaken under an atmosphere of hydrogen (50 psi) for 3 hours. The mixture was filtered and the solvent was evaporated under reduced pressure to give the title compound as a colorless gum (225 mg, 85%). ^{1}H NMR (360MHz, $CDCl_3$) δ 1.30 (3H, d, *J* 6.5 Hz) 1.54-1.64 (4H, m), 1.86-1.97 (2H, m), 2.21-2.30 (2H, m), 3.19 (1H, d, *J* 8.7 Hz), 3.27 (1H, d, *J* 8.7 Hz), 3.87-3.97 (4H, m), 4.24 (1H, q, *J* 6.5 Hz), 7.19-7.37 (5H, m), 7.50 (2H, s), and 7.71 (1H, s).

EXAMPLE 13

(*RS*)-1-{1-[(4-Oxo-1-phenylcyclohexyl)methoxy]ethyl}-3,5-bis(trifluoromethyl)benzene

Prepared from (*RS*)-1-{1-[(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)methoxy]ethyl]}-3,5-bis(trifluoromethyl)benzene (Example 12) according to the method of Example 10. ^{1}H NMR (360MHz, $CDCl_3$) δ 1.34 (3H, d, *J* 6.5 Hz) 2.03-2.15 (2H, m), 2.29-2.36 (4H, m), 2.51-2.60 (2H, m), 3.23 (1H, d, *J* 9.0 Hz), 3.31 (1H, d, *J* 9.0 Hz), 4.29 (1H, q, *J* 6.5 Hz), 7.27-7.31 (1H, m), 7.37-7.45 (4H, m), 7.51 (2H, s), and 7.73 (1H, s).

EXAMPLE 14

(*RS*)-β-[(1,4-Dioxa-8-phenylspiro[4.5]decan-8-yl)methoxy]-3,5-bis(trifluoromethyl) benzeneethanol

Borane tetrahydrofuran complex (1M in THF, 1.2 mL, 1.2 mmol) was added to a cooled (0 C) solution of 1-{1-[(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)methoxy]ethenyl]}-3,5-bis(trifluoromethyl)benzene (Description34, 280 mg, 0.6 mmol) in tetrahydrofuran (5 mL), and the mixture was stirred at room temperature for 48 hours. Aqueous sodium hydroxide (4M, 2 mL) followed by aqueous hydrogen peroxide (30%, 2 mL) were added and the mixture was stirred at room temperature for 1 hour. Water (20 mL) was added and the mixture was extracted with ethyl acetate (2 x 30 mL). The combined organic fractions were washed with brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the crude title compound as a colorless gum (263 mg), which was used without further purification.

EXAMPLE 15

(*RS*)-β-[(4-Oxo-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol

Prepared from (*RS*)-β-[(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol (Example 14) according to the method of Example 10. ^1H NMR (360MHz, $CDCl_3$) δ 1.75-1.79 (1H, m), 2.01-2.09 (2H, m), 2.32-2.37 (4H, m), 2.56-2.69 (2H, m), 3.37 (1H, d, *J* 8.8 Hz), 3.41 (1H, d, *J* 8.8 Hz), 3.53-3.57 (2H, m), 4.30-4.33 (1H, m), 7.31-7.35 (1H, m), 7.41-7.48 (4H, m), 7.52 (2H, s), and 7.79 (1H, s).

EXAMPLE 16

3,5-Bis(trifluoromethyl)phenylmethyl 4-Oxo-1-phenylcyclohexanecarboxylate

Oxalyl chloride (4.8 mL, 55 mmol) was added to a solution of 4-oxo-1-phenylcyclohexanecarboxylic acid (Description 2, 6 g, 27 mmol) and dimethylformamide (1 drop) in toluene (150 mL) and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure and toluene was added. The solvent was evaporated under reduced pressure and the residue was dissolved in toluene (100 mL). 3,5-Bis(trifluoromethyl)benzenemethanol (6.25 g, 26 mmol) and 4-dimethylaminopyridine (3.62 g, 30 mmol) were added and the mixture was heated under reflux for 24 hours. The solvent was evaporated under reduced pressure and the residue was partitioned between ethyl acetate (100 mL) and hydrochloric acid (2M, 100 mL). The organic layer was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with isohexane/CH_2Cl_2 (60:40 increasing to

50:50) to give the title compound (4.5 g, 40%). ^{1}H NMR (360MHz, $CDCl_3$) δ 2.33-2.53 (6H, m), 2.72-2.77 (2H, m), 5.23 (2H, s), 7.28-7.41 (5H, m), 7.51 (2H, s), and 7.77 (1H, s).

EXAMPLE 17

4-Oxo-1-phenyl-N-{[3,5-bis(trifluoromethyl)phenyl]methyl}cyclohexanecarboxamide

Prepared from 4-oxo-1-phenylcyclohexanecarboxylic acid (Description 2) and 3,5-bis(trifluoromethyl)benzylamine according to the method of Example 177. m/z (ES^+) 444 (M+1).

EXAMPLE 18

(*RS*)-4-Oxo-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl} cyclohexanecarboxamide

Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (2.18 g, 8.6 mmol) was added to a cooled (0 °C) solution of 4-oxo-1-phenylcyclohexanecarboxylic acid (Description 2, 1.33 g, 6.1 mmol) and triethylamine (2.55 mL, 1.85 g, 18.3 mmol) in dichloromethane (20 mL) and the mixture was stirred at room temperature for 20 minutes (*RS*)-α-methyl-3,5-bis(trifluoromethyl)benzenemethanamine (Description 5, 1.57 g, 6.1 mmol) in dichloromethane (10 mL) was added and the mixture was stirred at room temperature for 26 hours. The solvent was evaporated under reduced pressure and hydrochloric acid (2M, 50 mL) was added. The mixture was extracted with ethyl acetate (3 x 50 mL) and the combined organic fractions were washed with hydrochloric acid (2M, 2 x 50 mL), aqueous sodium hydrogen carbonate (saturated, 2 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with isohexane/EtOAc (65:35), to give the title compound as a colorless foam (1.96 g, 70%). m/z (ES^+) 458 (M+1).

EXAMPLE 19

N-[(8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)methyl]-3,5-bis(trifluoromethyl) benzenemethanamine

Sodium triacetoxyborohydride (4.77 g, 22.5 mmol) was added to a solution of 8-phenyl-1,4-dioxaspiro[4.5]decane-8-carboxaldehyde (*J.Med.Chem.* **1975**, *18*, 593-599). (1.1 g, 4.5 mmol) and 3,5-bis(trifluoromethyl)benzenemethanamine (1.1 g, 4.5 mmol) in dichloroethane (50 mL) and the mixture was stirred at room temperature overnight. The mixture was poured into saturated aqueous sodium hydrogen carbonate (50 mL) and extracted with ethyl acetate (2 x 50 mL). The combined organic fractions were washed with brine (50 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash

column chromatography on silica gel, eluting with isohexane/EtOAc (75:25), to give the title compound as a yellow oil (1.0 g, 47%). m/z (ES^+) 473 (M+1).

EXAMPLE 20

N-[(8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)methyl]-N-{[3,5-bis(trifluoromethyl)phenyl] methyl}acetamide

Acetic anhydride (2 mL) was added to a solution of N-[(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)methyl]-3,5-bis(trifluoromethyl)benzenemethanamine (Example 19, 291 mg, 0.61 mmol) in pyridine (5 mL) and the mixture was stirred at room temperature for 1 hour. The solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (25 mL). The mixture was washed with aqueous copper sulphate (5%, 2 x 25 mL) and brine (25 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound (316 mg, 100%). m/z (ES^+) 516 (M+1).

EXAMPLE 21

N-[(4-Oxo-1-phenylcyclohexyl)methyl]-N-{[3,5-bis(trifluoromethyl)phenyl]methyl} acetamide

Prepared from N-[(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)methyl]-N-{[3,5-bis(trifluoromethyl)phenyl]methyl}acetamide (Example 20) according to the method of Example 10. ^{1}H NMR (400MHz, $CDCl_3$) mixture of two rotamers; major rotamer δ 7.76 (1H, s), 7.50-7.39 (5H, m), 7.20 (2H, s), 3.71 (2H, s), 3.56 (2H, s), 2.75-2.10 (8H, m), and 2.07 (3H, s); minor rotamer δ 7.72 (1H, s), 7.50-7.39 (5H, m), 7.31 (2H, s), 4.24 (2H, s), 3.43 (2H, s), 2.75-2.10 (8H, m), and 1.83 (3H, s).

EXAMPLE 22

(*E*)-4-Phenyl-4-{3-[3,5-bis(trifluoromethyl)phenyl]prop-1-enyl}cyclohexanone

Prepared from 8-phenyl-8-{3-[3,5-bis(trifluoromethyl)phenyl] prop-1-enyl}1,4-dioxaspiro[4.5]decane (Description 35) according to the method of Example 10. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.71 (1H, s), 7.62 (2H, s), 7.46-7.28 (5H, m), 5.75 (1H, d, *J* 15.4 Hz), 5.49 (1H, dt, J_t 15.4, J_d 7.1 Hz), 3.49 (2H, d, *J* 7.1 Hz), 2.46 (6H, m), and 2.20 (2H, m).

EXAMPLE 23

(*RS*)-1-(8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)-3-[3,5-bis(trifluoromethyl)phenyl] propan-2-yl Ethanoate and

(*RS*)-1-(8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)-3-[3,5-bis(trifluoromethyl)phenyl] propan-1-yl Ethanoate

Borane-tetrahydrofuran complex (1.0M in tetrahydrofuran, 12 mL, 12 mmol) was added over 10 minutes to a solution of (*E*)-8-phenyl-8-{3-[3,5-bis(trifluoromethyl)phenyl]prop-1-enyl}1,4-dioxaspiro[4.5]decane (Description 35, 1.88 g, 4 mmol) and the mixture was stirred at room temperature for 4.5 hours. Water (2 mL) then aqueous sodium hydroxide (4M, 20 mL) and aqueous hydrogen peroxide (30 w/v%, 20 mL) were added and the mixture was stirred at room temperature for 30 minutes. Water (150 mL) was added and the mixture was extracted with ether (2 x 150 mL). The combined organic fractions were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was dissolved in pyridine (10 mL) and 4-dimethylaminopyridine (10 mg) and acetic anhydride (5 mL) were added. The mixture was stirred at room temperature for 4 hours, then water (150 mL) was added. The mixture was extracted with ethyl acetate (2 x 150 mL) and the combined organic fractions were washed with water (2 x 150 mL) and aqueous copper sulfate (5%, 2 x 100 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/EtOAc (99:1 increasing to 95:5), to give:

(RS)-*1-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)-3-[3,5-bis(trifluoromethyl)phenyl] propan-2-yl ethanoate* (803 mg, 38%); ^{1}H NMR (360MHz, $CDCl_3$) δ 7.67 (1H, s), 7.36 (2H, s), 7.28-7.13 (5H, m), 4.87 (1H, m), 3.90 (4H, m), 2.68 (1H, dd, *J* 13.7, 6.7 Hz), 2.45 (1H, dd, *J* 13.7, 6.2 Hz), 2.23 (2H, m), 1.96 (1H, dd, *J* 14.7, 7.4 Hz), 1.80-1.45 (7H, m), and 1.72 (3H, m); and

(RS)-*1-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)-3-[3,5-bis(trifluoromethyl)phenyl] propan-1-yl ethanoate* (425 mg, 20%); ^{1}H NMR (360MHz, $CDCl_3$) δ 7.66 (1H, s), 7.44 (2H, s), 7.35-7.20 (5H, m), 4.98 (1H, dd, *J* 10.1, 2.1 Hz), 3.89 (4H, m), 2.51 (2H, m), 2.24 (2H, m), 2.06 (3H, s), and 1.95-1.40 (8H, m).

EXAMPLE 24

(*RS*)-1-(8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)-3-[3,5-bis(trifluoromethyl)phenyl] propan-2-ol

Potassium carbonate (2.5 g) was added to a solution of (*RS*)-1-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)-3-[3,5-bis(trifluoromethyl)phenyl]propan-2-yl ethanoate (Example 23, 700 mg, 1.3 mmol) in methanol (20 mL) and water (3 mL) and the mixture was stirred at

room temperature for 4 days. The methanol was evaporated under reduced pressure , water (50 mL) was added and the mixture was extracted with ethyl acetate (3 x 75 mL). The combined organic fractions were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound as a colorless oil (626 mg, 97%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.68 (1H, s), 7.49 (2H, s), 7.34 (4H, m), 7.22 (1H, m), 3.91 (4H, m), 3.75 (1H, m), 2.66 (1H, dd, *J* 13.8, 8.2 Hz), 2.56 (1H, dd, *J* 13.8, 4.5 Hz), 2.33 (4H, m), and 1.89-1.49 (4H, m).

EXAMPLE 25

(*RS*)-4-{2-Hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]propyl}-4-phenylcyclohexanone

Prepared from (*RS*)-1-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)-3-[3,5-bis(trifluoromethyl)phenyl] propan-2-ol (Example 24) according to the method of Example 10. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.70 (1H, s), 7.48 (2H, s), 7.42 (3H, m), 7.29 (2H, m), 3.72 (1H, m), 2.76-2.56 (4H, m), 2.33 (4H, m), and 2.03-1.77 (4H, m).

EXAMPLE 26

Trans-(*RS*)-1-({4-[4-(4-Fluorophenyl)piperidin-1-yl]-α-methyl-1-phenylcyclohexanemethoxy}methyl)-3,5-bis(trifluoromethyl)benzene

Prepared from (*RS*)-1-[(α-methyl-4-oxo-1-phenylcyclohexanemethoxy)methyl]-3,5-bis(trifluoromethyl)benzene (Example 6) and 4-(4-fluorophenyl)piperidine (Description 16) according to the method of Example 55. The product was purified by preparative thin layer chromatography on silica gel, eluting with CH_2Cl_2/MeOH/Et_3N(Aq.) (95:5:1).
m/z (ES^+) 608 (M+1).

EXAMPLE 27

Cis-(*RS*)-1-({α-Ethenyl-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanemethoxy}methyl)-3,5-bis(trifluoromethyl)benzene and *Trans*-(*RS*)-1-({α-Ethenyl-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanemethoxy}methyl)-3,5-bis(trifluoromethyl)benzene

Prepared from (*RS*)-1-[(α-ethenyl-4-oxo-1-phenylcyclohexanemethoxy)methyl]-3,5-bis(trifluoromethyl)benzene (Example 8) and 4-(4-fluorophenyl)piperidine (Description 16) according to the method of Example 55. The product was purified by preparative thin layer chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_3(Aq.) (95:5:1):
trans-(RS)-*1-({4-[4-(4-fluorophenyl)piperidin-1-yl]-α-ethenyl-1-phenylcyclohexanemethoxy}methyl)-3,5-bis(trifluoromethyl)benzene*; ^{1}H NMR (400MHz,

$CDCl_3$) δ 1.21-1.41 (2H, m), 1.50-1.90 (8H, m), 2.20-2.26 (2H, m), 2.35-2.45 (3H, m), 2.63-2.68 (1H, m), 2.90-2.93 (2H, m), 3.37 (1H, d, *J* 8.4 Hz), 4.23 (1H, d, *J* 12.6 Hz), 4.53 (1H, d, *J* 12.6 Hz), 5.17 (1H, d, *J* 18.8 Hz), 5.25-5.29 (1H, m), 5.42-5.51 (1H, m), 6.91-6.99 (2H, m), 7.10-7.42 (7H, m), 7.61 (2H, s), and 7.74 (1H, s); m/z (ES^+) 620 (M+1);

cis-(RS)-*1-({4-[4-(4-fluorophenyl)piperidin-1-yl]-α-ethenyl-1-phenylcyclohexanemethoxy}methyl)-3,5-bis(trifluoromethyl)benzene*; ^1H NMR (400MHz, $CDCl_3$) δ 1.44-1.68 (10H, m), 2.10-2.31 (4H, m), 2.42-2.50 (1H, m), 2.75-2.83 (1H, m), 3.05-3.15 (2H, m), 4.07-4.11 (1H, m), 4.38 (1H, d, *J* 13.2 Hz), 4.61 (1H, d, *J* 13.2 Hz), 5.18-5.28 (3H, m), 6.95-6.99 (2H, m), 7.16-7.44 (7H, m), 7.74 (2H, s), and 7.76 (1H, s); m/z (ES^+) 620 (M+1).

EXAMPLE 28

Trans-(*RS*)-4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenyl-α-[3,5-bis(trifluoromethyl) phenylmethoxy]cyclohexaneethanol

Ozone was bubbled through a stirred, cooled (-78 °C) solution of *trans*-(*RS*)-1-({4-[4-(4-fluorophenyl)piperidin-1-yl]-α-ethenyl-1-phenylcyclohexanemethoxy}methyl)-3,5-bis(trifluoromethyl)benzene (Example 27, 240 mg, 0.39 mmol) in dichloromethane (50 mL) and methanol (20 mL) for 5 minutes. Sodium borohydride (140 mg, 3.9 mmol) and methanol (50 mL) were added and the mixture was allowed to warm to room temperature. The solvent was evaporated under reduced pressure and ethyl acetate (50 mL) and aqueous sodium bicarbonate (saturated, 50 mL) were added. The layers were separated and the organic fraction was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/MeOH (90:10) to give the title compound (52 mg, 21%). m/z (ES^+) 624 (M+1).

EXAMPLE 29

Trans-(*RS*)-1-({α-Ethyl-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanemethoxy}methyl)-3,5-bis(trifluoromethyl)benzene

A slurry of palladium on carbon (10%, 20 mg) in methanol (10 mL) was added to a solution of *trans*-(*RS*)-1-({α-ethenyl-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanemethoxy}methyl)-3,5-bis(trifluoromethyl)benzene (Example 27, 90 mg, 0.14 mmol) in methanol (15 mL) and the mixture was shaken under an atmosphere of hydrogen (50 psi) for 16 hours. The mixture was filtered through Celite™ and the solvent was evaporated under reduced pressure to give the title compound as a colorless oil (88 mg, 98%). m/z (ES^+) 622 (M+1).

EXAMPLE 30

Trans-1-[({4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methoxy)methyl]-2-methoxybenzene

A solution of sodium cyanoborohydride (83 mg, 1.3 mmol) and zinc chloride (90 mg, 0.66 mmol) in methanol (10 mL) and added to a solution of 1-({[4-oxo-1-phenylcyclohexyl]methoxy}methyl)-2-methoxybenzene (Example 2, 400 mg, 1.3 mmol) and 4-(4-fluorophenyl)piperidine (Description 16, 256 mg, 1.43 mmol) in methanol (10 mL) and the mixture was stirred at room temperature for 24 hours. The mixture was poured into saturated aqueous sodium hydrogen carbonate (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_3(Aq.) (98:2:0.2), to give the title compound. m/z (ES^+) 488 (M+1).

EXAMPLE 31

Trans-1-[({4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methoxy)methyl]-2-(cyclopropoxy)-5-(trifluoromethoxy)benzene

Prepared from 1-({[4-oxo-1-phenylcyclohexyl]methoxy}methyl)-2-(cyclopropoxy)-5-(trifluoromethoxy)benzene (Example 4) and 4-(4-fluorophenyl)piperidine (Description 16) according to the method of Example 55. m/z (ES^+) 598 (M+1).

EXAMPLE 32

Cis-(*RS*)-1-[1-({4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methoxy) ethyl]-3,5-bis(trifluoromethyl)benzene and

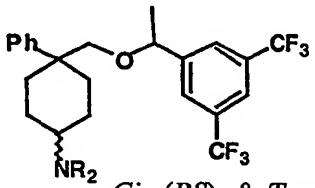
Trans-(*RS*)-1-[1-({4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methoxy) ethyl]-3,5-bis(trifluoromethyl)benzene

Prepared from (*RS*)-1-{1-[(4-oxo-1-phenylcyclohexyl) methoxy]ethyl}-3,5-bis(trifluoromethyl)benzene (Example 13) and 4-(4-fluorophenyl)piperidine (Description 16) according to the method of Example 55:

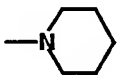
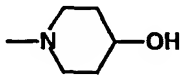
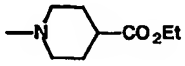
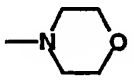
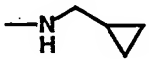
Cis-(RS)-*1-[1-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methoxy) ethyl]-3,5-bis(trifluoromethyl)benzene*; ^{1}H NMR (400MHz, $CDCl_3$) δ 1.32 (3H, d, *J* 6.5 Hz), 1.43-1.90 (10H, m), 2.20-2.40 (4H, m), 2.44-2.50 (2H, m), 3.07-3.09 (2H, m), 3.45 (1H, d, *J* 9.2 Hz), 3.58 (1H, d, *J* 9.2 Hz), 4.28 (1H, q, *J* 6.5 Hz), 6.95-7.00 (2H, m), 7.16-7.30 (4H, m), 7.31-7.38 (3H, m), 7.51 (2H, s), and 7.72 (1H, s); m/z (ES^+) 608 (M+1);

Trans-(RS)-*1-[1-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methoxy) ethyl]-3,5-bis(trifluoromethyl)benzene*; ^{1}H NMR (360MHz, $CDCl_3$) δ 1.32 (3H, d, *J* 6.5 Hz), 1.42-1.83 (10H, m), 2.10-2.20 (2H, m), 2.32-2.44 (4H, m), 2.90-3.00 (2H, m), 3.10 (1H, d, *J* 8.9 Hz), 3.16 (1H, d, *J* 8.9 Hz), 4.23 (1H, q, *J* 6.5 Hz), 6.93 (2H, t, *J* 8.6 Hz), 7.10-7.22 (2H, m), 7.25-7.36 (5H, m), 7.52 (2H, s), and 7.72 (1H, s); m/z (ES^+) 608 (M+1).

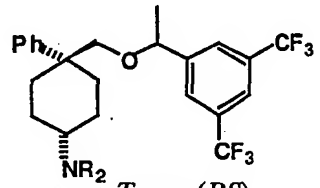
The following compounds were prepared as mixtures of *cis*- and *trans*-isomers from (*RS*)-1-{1-[(4-oxo-1-phenylcyclohexyl)methoxy]ethyl}-3,5-bis(trifluoromethyl)benzene (Example 13) according to the method of Example 55, substituting a suitable amine for piperidine.



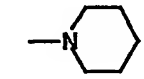
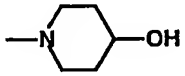
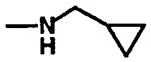
Cis-(*RS*)- & *Trans*-(*RS*)-

Ex.	-NR_2	Formula	M.W.	m/z (ES^+) (M+1).
33		C28H33F6NO	513	514
34		C28H33F6NO2	529	530
35		C31H37F6NO3	585	586
36		C27H31F6NO2	515	516
37		C27H31F6NO	499	500
38		C25H29F6NO	473	474

The following *trans*-isomers were prepared from the compounds of Examples 33, 34, 37 and 38 by preparative thin layer chromatography on silica gel, eluting with CH_2Cl_2/MeOH/Et_3N (95:5:1).



Trans-(*RS*)-

Ex.	-NR_2	Formula	M.W.	m/z (ES^+) (M+1).
39		C28H33F6NO	513	514
40		C28H33F6NO2	529	530
41		C27H31F6NO	499	500
42		C25H29F6NO	473	474

EXAMPLE 43

Cis-(*RS*)-β-[(4-Hydroxy-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl) benzeneethanol and

Trans-(*RS*)-β-[(4-Hydroxy-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl) benzeneethanol

Sodium borohydride (25 mg, 0.65 mmol) was added to a solution of (*RS*)-β-[(4-oxo-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol (Example 15, 75 mg, 0.16 mmol) in ethanol (5 mL) and the mixture was stirred at room temperature for 25 minutes. The solvent was evaporated under reduced pressure and ethyl acetate (50 mL) and hydrochloric acid (2M, 50 mL) were added. The layers were separated and the organic fraction was washed with brine (50 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by MPLC column chromatography on silica gel, eluting with CH_2Cl_2/EtOAc (80:20) to give:

trans-(RS)-*β-[(4-hydroxy-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl) benzeneethanol* (34 mg, 46%); ^1H NMR (400MHz, CD_3OD) δ 1.21-1.35 (2H, m), 1.62-1.82

(4H, m), 2.31-2.35 (1H, m), 2.47-2.51 (1H, m), 3.24 (1H, d, *J* 8.8 Hz), 3.36 (1H, d, *J* 8.8 Hz), 3.49-3.65 (3H, m), 4.31 (1H, t, *J* 5.4 Hz), 7.16-7.20 (1H, m), 7.28-7.32 (2H, m), 7.40-7.42 (2H, m), 7.64 (2H, s), and 7.80 (1H, s); and

cis-(RS)-*β-[(4-hydroxy-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl) benzeneethanol* (10 mg, 14%); ^{1}H NMR (400MHz, CD_3OD) δ 1.49-1.70 (4H, m), 1.80-1.85 (1H, m), 1.91-1.95 (1H, m), 2.07-2.14 (1H, m), 2.20-2.26 (1H, m), 3.37 (1H, d, *J* 8.8 Hz), 3.49-3.61 (3H, m), 3.69-3.71 (1H, m), 4.34 (1H, t, *J* 5.6 Hz), 7.15-7.19 (1H, m), 7.26-7.29 (2H, m), 7.38-7.40 (2H, m), 7.65 (2H, s), and 7.80 (1H, s).

EXAMPLE 44

Cis-(RS)-β-({4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methoxy)-3,5-bis(trifluoromethyl)benzeneethanol and

Trans-(RS)-β-({4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methoxy)-3,5-bis(trifluoromethyl)benzeneethanol

Prepared from (*RS*)-β-[(4-oxo-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl) benzeneethanol (Example 15) and 4-(4-fluorophenyl) piperidine (Description 16) according to the method of Example 55:

Cis-(RS)-*β-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl} methoxy)-3,5-bis(trifluoromethyl)benzeneethanol*; ^{1}H NMR (360MHz, $CDCl_3$) δ 1.46-1.78 (6H, m), 1.80-2.06 (6H, m), 2.20-58 (6H, m), 3.04-3.30 (1H, m), 3.42-3.64 (3H, m), 3.68-3.76 (1H, m), 6.97 (2H, t, *J* 8.7 Hz), 7.17-7.21 (3H, m), 7.32-7.39 (4H, m), 7.57 (2H, s), and 7.79 (1H, s); m/z (ES^+) 624 (M+1);

Trans-(RS)-*β-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl} methoxy)-3,5-bis(trifluoromethyl)benzeneethanol*; ^{1}H NMR (360MHz, $CDCl_3$) δ 1.21-1.98 (13H, m), 2.21-2.58 (4H, m), 2.58-2.68 (1H, m), 2.97-3.12 (1H, m), 3.22 (1H, d, *J* 8.7 Hz), 3.28 (1H, d, *J* 8.7 Hz), 3.51 (1H, m), 4.24-4.30 (1H, m), 6.95 (2H, t, *J* 8.7 Hz), 7.10-7.15 (2H, m), 7.25 (1H, s), 7.37-7.38 (4H, m), 7.53 (2H, s), and 7.78 (1H, s); m/z (ES^+) 624 (M+1).

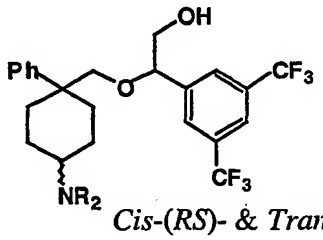
EXAMPLE 45

Cis- and *Trans-(RS)*-β-{[1-Phenyl-4-(phenylmethylamino)cyclohexyl]methoxy}-3,5-bis(trifluoromethyl)benzeneethanol

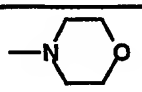
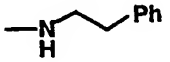
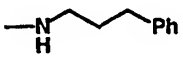
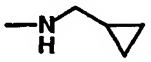
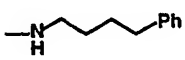
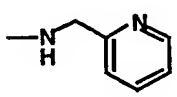
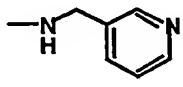
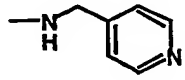
Sodium triacetoxyborohydride (98 mg, 0.46 mmol) and glacial acetic acid (19 mg, 0.33 mmol) were added to a solution of (*RS*)-β-[(4-oxo-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol (Example 15, 156 mg, 0.33 mmol) and benzylamine (35 mg, 0.33 mmol) in dichloroethane (3 mL) and the mixture was stirred at room temperature

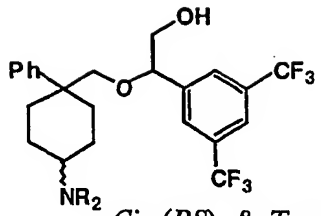
overnight. Aqueous sodium hydrogen carbonate (saturated, 3 mL) and dichloromethane (5 mL) were added and the layers were separated. The organic fraction was poured onto an SCX cartridge (Varian Bond Elut™; 10 mL/500 mg) and the cartridge was washed with methanol (4 x 2 mL), then eluted with methanolic ammonia (2M, 2 x 2 mL). The solvent was evaporated under reduced pressure to give the title compound as a colorless solid (151 mg, 83%). ^{1}H NMR and analytical HPLC showed this to be a 1:1 mixture of *trans*:*cis* isomers. m/z (ES^+) 552 (M+1).

The following compounds were prepared as mixtures of *cis*- and *trans*-isomers from (*RS*)-β-[(4-oxo-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol (Example 15) according to the method of Example 45, substituting a suitable amine for benzylamine.

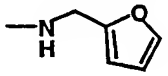


Cis-(*RS*)- & *Trans*-(*RS*)-

Ex.	-NR_2	Formula	M.W.	m/z (ES^+) (M+1).
46		C27H31F6NO3	531	532
47		C31H33F6NO2	565	566
48		C32H35F6NO2	579	580
49		C27H31F6NO2	515	516
50		C33H37F6NO2	593	594
51		C29H30F6N2O2	552	553
52		C29H30F6N2O2	552	553
53		C29H30F6N2O2	552	553



Cis-(*RS*)- & *Trans*-(*RS*)-

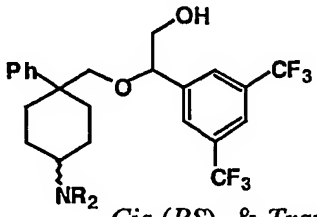
Ex.	-NR_2	Formula	M.W.	m/z (ES^+) (M+1).
54		C28H29F6NO3	541	542

EXAMPLE 55

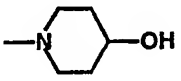
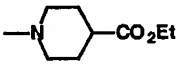
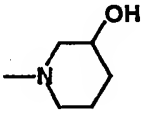
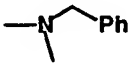
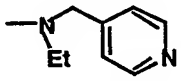
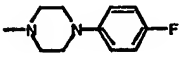
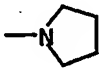
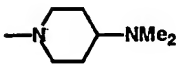
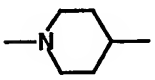
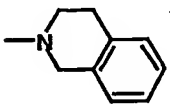
Cis- and *Trans*-(*RS*)-β-[(1-Phenyl-4-(piperidin-1-yl)cyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol

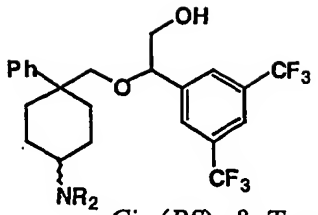
A mixture of sodium cyanoborohydride (6.8 mg, 0.11 mmol) and zinc chloride (7.3 mg, 0.05 mmol) in methanol (2 mL) was added to a solution of (*RS*)-β-[(4-oxo-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol (Example 15, 25 mg, 0.05 mmol) and piperidine (16 μl, 0.05 mmol) in methanol (2 mL) and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure and aqueous sodium hydrogen carbonate (saturated, 3 mL) and dichloromethane (5 mL) were added. The layers were separated and the organic fraction was poured onto an SCX cartridge (Varian Bond Elut™; 10 mL/500 mg). The cartridge was washed with methanol (4 x 2 mL), then eluted with methanolic ammonia (2M, 2 x 2 mL). The solvent was evaporated under reduced pressure to give the title compound as a colorless solid (20 mg, 70%). ^1H NMR and analytical HPLC showed this to be a 1:1 mixture of *trans*:*cis* isomers. m/z (ES^+) 530 (M+1).

The following compounds were prepared as mixtures of *cis*- and *trans*-isomers from (*RS*)-β-[(4-oxo-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol (Example 15) according to the method of Example 55, substituting a suitable amine for piperidine.

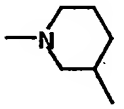
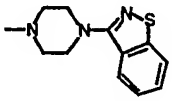
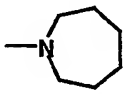
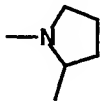
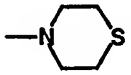
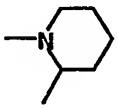
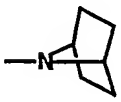
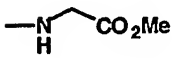
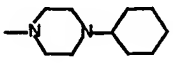
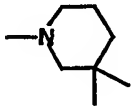
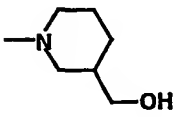


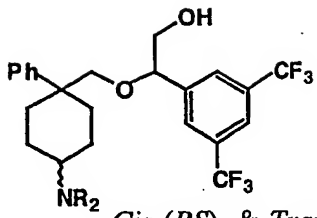
Cis-(*RS*)- & *Trans*-(*RS*)-

Ex.	-NR_2	Formula	M.W.	m/z (ES^+) (M+1).
56		C28H33F6NO3	545	546
57		C31H37F6NO4	601	602
58		C28H33F6NO3	545	546
59		C31H33F6NO2	565	566
60		C31H34F6N2O2	580	581
61		C33H35F7N2O2	624	625
62		C27H31F6NO2	515	516
63		C24H27F6NO2	475	476
64		C30H38F6N2O2	572	573
65		C29H35F6NO2	543	544
66		C32H33F6NO2	577	578

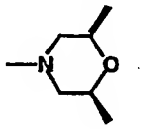
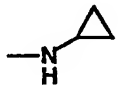


Cis-(*RS*)- & *Trans*-(*RS*)-

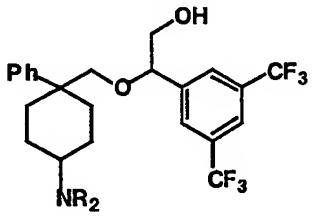
Ex.	-NR_2	Formula	M.W.	m/z (ES^+) (M+1).
67		C29H35F6NO2	543	544
68		C34H35F6N3O2S	663	664
69		C29H35F6NO2	543	544
70		C28H33F6NO2	529	530
71		C27H31F6NO2S	547	548
72		C29H35F6NO2	543	544
73		C29H33F6NO2	541	542
74		C26H29F6NO4	533	534
75		C33H42F6N2O2	612	613
76		C30H37F6NO2	557	558
77		C29H35F6NO3	559	560

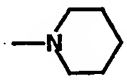
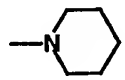
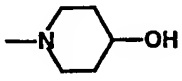
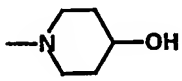
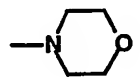


Cis-(RS)- & Trans-(RS)-

Ex.	-NR_2	Formula	M.W.	m/z (ES^+) (M+1).
78		C29H35F6NO3	559	560
79		C26H29F6NO2	501	502

The following isomers were prepared from the compounds of Examples 55, 56 and 46 by MPLC chromatography on silica gel, eluting with CH_2Cl_2/MeOH/Et_3N (95:5:0.2).



Ex.	-NR_2	Stereochemistry	Formula	M.W.	m/z (ES^+) (M+1).
80		*Cis-(RS)-*	C28H33F6NO2	529	530
81		*Trans-(RS)-*	C28H33F6NO2	529	530
82		*Cis-(RS)-*	C28H33F6NO3	545	546
83		*Trans-(RS)-*	C28H33F6NO3	545	546
84		*Trans-(RS)-*	C27H31F6NO3	531	532

EXAMPLE 85

Trans-(*RS*)-β-{[1-Phenyl-4-(phenylmethylamino)cyclohexyl]methoxy}-3,5-bis(trifluoromethyl)benzeneethanol Hydrochloride and

Cis-(*RS*)-β-{[1-Phenyl-4-(phenylmethylamino)cyclohexyl]methoxy}-3,5-bis(trifluoromethyl)benzeneethanol Hydrochloride

Benzylamine (1.07 mL, 9.8 mmol) was added to a mixture of (*RS*)-β-[(4-oxo-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol (Example 15, 1.5 g, 3.2 mmol) and dry alumina (1 g) in ethanol (35 mL) and the mixture was heated under reflux overnight. The mixture was cooled, filtered and cooled to –78 °C. Sodium borohydride (1.23 g, 32.6 mmol) was added in portions over 2 hours, then aqueous sodium hydrogen carbonate (saturated, 20 mL) was added and the mixture was warmed to room temperature. The solvent was evaporated under reduced pressure and ethyl acetate (50 mL) and water (50 mL) were added. The layers were separated and the organic fraction was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH/Et_3N (98:2:1) to give a 5:1 mixture of *trans*:*cis* isomers (1.48 g), which was dissolved in ethyl acetate:hexane (3:1, 13 mL) and treated with ethereal hydrogen chloride (1M, 2.7 mL). The solid was collected and dried *in vacuo* to give:

trans-(RS)-*β-{[1-phenyl-4-(phenylmethylamino)cyclohexyl]methoxy}-3,5-bis(trifluoromethyl)benzeneethanol hydrochloride* (1.3 g, 72%). ^{1}H NMR (400MHz, CD_3OD) δ 1.43-1.54 (2H, m), 1.73-1.82 (2H, m), 2.05-2.18 (2H, m), 2.50-2.58 (1H, m), 2.67-2.71 (1H, m), 2.82-2.88 (1H, m), 3.24 (1H, d, *J* 8.6 Hz), 3.37 (1H, d, *J* 8.6 Hz), 3.53-3.64 (2H, m), 4.13 (2H, s), 4.34 (1H, t, *J* 5.0 Hz), 7.20-7.24 (1H, m), 7.33-7.45 (9H, m), 7.65 (2H, s), and 7.81 (1H, s). m/z (ES^+) 552 (M+1).

The mother liquors from the recrystallisation were collected and the solvent was evaporated under reduced pressure. The residue was crystallised from ethanol/water (70:30) and the solid was collected and dried *in vacuo* to give:

cis-(RS)-*β-{[1-phenyl-4-(phenylmethylamino)cyclohexyl]methoxy}-3,5-bis(trifluoromethyl)benzeneethanol hydrochloride* (50 mg, 3%). ^{1}H NMR (400MHz, CD_3OD) δ 1.39-1.70 (4H, m), 1.81-1.90 (2H, m), 2.15-2.18 (1H, m), 2.36-2.39 (1H, m), 2.56-2.60 (1H, m), 3.48-3.61 (3H, m), 3.84 (1H, d, *J* 8.6 Hz), 3.77 (2H, s), 4.37 (1H, t, *J* 5.0 Hz), 7.18-7.48 (10H, m), 7.64 (2H, s), and 7.80 (1H, s). m/z (ES^+) 552 (M+1).

EXAMPLE 86

Trans-(RS)-β-{[1-Phenyl-4-(phenylmethylamino)cyclohexyl]methoxy}-3,5-bis(trifluoromethyl)benzeneethanol

A sample of *trans*-(*RS*)-β-{[1-phenyl-4-(phenylmethylamino)cyclohexyl]methoxy}-3,5-bis(trifluoromethyl)benzeneethanol hydrochloride (Example 85) was suspended in aqueous sodium hydrogen carbonate (saturated) and the mixture was extracted with ethyl acetate (3 x). The combined organic fractions were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound. ^1H NMR (400MHz, CD_3OD) δ 1.17-1.29 (2H, m), 1.58-1.68 (2H, m), 1.83-1.89 (2H, m), 2.36-2.40 (1H, m), 2.53-2.65 (2H, m), 3.21 (1H, d, *J* 8.0 Hz), 3.33 (1H, d, *J* 8.0 Hz), 3.51 (1H, dd, *J* 10.8, 4.8 Hz), 3.61 (1H, dd, *J* 10.8, 5.6 Hz), 3.72 (2H, s), 4.30 (1H, t, *J* 5.2 Hz), 7.15-7.30 (8H, m), 7.40-7.42 (2H, m), 7.63 (2H, s), and 7.79 (1H, s).

EXAMPLE 87

Trans-(*RS*)-β-[(4-Amino-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl) benzeneethanol

A slurry of palladium on carbon (5%, 20 mg) in methanol (10 mL) was added to a solution of *trans*-(*RS*)-β-{[1-phenyl-4-(phenylmethylamino)cyclohexyl]methoxy}-3,5-bis(trifluoromethyl)benzeneethanol hydrochloride (Example 85, 79 mg, 0.13 mmol) in ethanol (4 mL) and the mixture was shaken under an atmosphere of hydrogen (50 psi) for 16 hours. The mixture was filtered through Celite™, washing with ethanol, and the solvent was evaporated under reduced pressure. The residue was crystallised from Et_2O/EtOAc (2:1, 1 mL) and the solid was collected and dried *in vacuo* to give the title compound as a colorless solid (25 mg, 37%). m/z (ES^+) 462 (M+1).

EXAMPLE 88

Cis-(*RS*)-β-[(4-Amino-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl) benzeneethanol

Prepared from *cis*-(*RS*)-β-{[1-phenyl-4-(phenylmethylamino)cyclohexyl]methoxy}-3,5-bis(trifluoromethyl)benzeneethanol hydrochloride (Example 85) according to the method of Example 87. m/z (ES^+) 462 (M+1).

EXAMPLE 89

Trans-(*RS*)-β-({4-[N-Methyl(phenylmethyl)amino]-1-phenylcyclohexyl}methoxy)-3,5-bis(trifluoromethyl)benzeneethanol

Prepared from *trans*-(*RS*)-β-{[1-phenyl-4-(phenylmethylamino)cyclohexyl]methoxy}-3,5-bis(trifluoromethyl)benzeneethanol (Example 86) according to the method of Example 212. m/z (ES^+) 566 (M+1).

EXAMPLE 90

Trans-(*RS*)-β-[(4-Methylamino-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl) benzeneethanol

Prepared from *trans*-(*RS*)-β-({4-[N-methyl(phenylmethyl)amino]-1-phenylcyclohexyl} methoxy)-3,5-bis(trifluoromethyl)benzeneethanol (Example 89) according to the method of Example 87. m/z (ES^+) 476 (M+1).

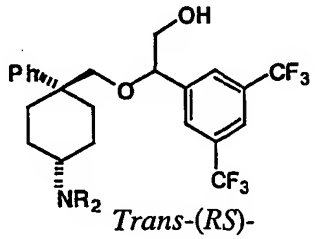
EXAMPLE 91

Trans-(*RS*)-β-[(4-{N-[2-(Dimethylamino)acetyl]amino}-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol

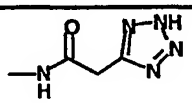
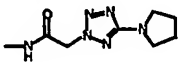
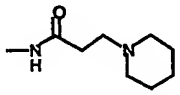
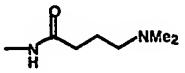
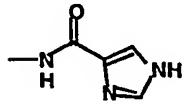
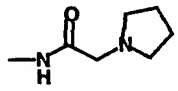
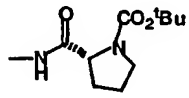
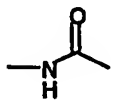
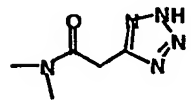
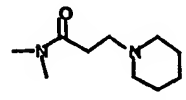
Triethylamine (25 μL, 0.18 mmol) was added to a mixture of *trans*-(*RS*)-β-[(4-amino-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol (Example 87, 30 mg, 0.06 mmol), N,N-dimethylglycine (18 mg, 0.15 mmol), 1-hydroxybenzotriazole (8 mg, 0.06 mmol) and 1-(dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (15 mg, 0.08 mmol) in dry dichloromethane (3 mL) and the mixture was stirred at room temperature overnight. Aqueous sodium hydroxide (0.05M, 3 mL) and dichloromethane (5 mL) were added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 x 3 mL) and the combined organic fractions were poured onto an SCX cartridge (Varian Bond Elut™; 10 mL/500 mg). The cartridge was washed with methanol (4 x 2 mL), then eluted with methanolic ammonia (2M, 2 x 2 mL) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on a short column of silica gel, eluting with CH_2Cl_2/MeOH/Et_3N (100:0:1 increasing to 90:10:1), to give the title compound as a colorless solid (12 mg, 36%). m/z (ES^+) 547 (M+1).

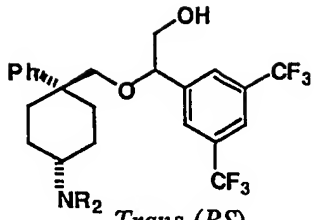
The following compounds were prepared from *trans*-(*RS*)-β-[(4-amino-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol (Example 87) or *trans*-(*RS*)-β-[(4-methylamino-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)

benzeneethanol (Example 90) according to the method of Example 91, substituting a suitable acid for N,N-dimethylglycine.

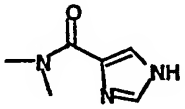
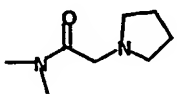


Trans-(RS)-

Ex.	-NR_2	Formula	M.W.	m/z (ES^+) (M+1).
92		C26H27F6N5O3	571	572
93		C30H34F6N6O3	640	641
94		C31H38F6N2O3	600	601
95		C29H36F6N2O3	574	575
96		C27H27F6N3O3	555	556
97[1]		C29H34F6N2O3	572	573
98		C33H40F6N2O5	658	659
99		C25H27F6NO3	503	504
100		C27H29F6N5O3	585	586
101		C32H40F6N2O3	614	615



Trans-(*RS*)-

Ex.	-NR_2	Formula	M.W.	m/z (ES^+) (M+1).
102		C28H29F6N3O3	569	570
103		C30H36F6N2O3	586	587

[1] 1-Pyrrolidineacetic acid: WO 9519344.

EXAMPLE 104

Trans-(*RS,S*)-N-(1-{[α-Hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy]methyl}-1-phenylcyclohexyl)-2-pyrrolidinecarboxamide

Trifluoroacetic acid (4 drops) was added to a solution of *trans*-(*RS,S*)-1,1-dimethylethyl 2-[(1-{[α-hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy]methyl}-1-phenyl cyclohexylamino)carbonyl]-1-pyrrolidinecarboxylate (Example 98, 5 mg, 8 μmol) in dichloromethane (3 mL) and the mixture was stirred at room temperature for 5 minutes. Aqueous sodium hydrogen carbonate (saturated, 3 mL) and dichloromethane (5 mL) were added and the layers were separated. The aqueous layer was extracted with dichloromethane (3 x 3 mL) and the combined organic fractions were poured onto an SCX cartridge (Varian Bond Elut™; 10 mL/500 mg). The cartridge was washed with methanol (4 x 2 mL), then eluted with methanolic ammonia (2M, 2 x 2 mL) and the solvent was evaporated under reduced pressure to give the title compound as a colorless solid (3 mg, 70%).

m/z (ES^+) 559 (M+1).

EXAMPLE 105

Cis- and *Trans*-(*RS*)-β-[(1-Phenyl-4-dimethylaminocyclohexyl)methoxyl-3,5-bis(trifluoromethyl)benzeneethanol

A slurry of palladium on carbon (5%, 20 mg) in methanol (10 mL) was added to a solution of (*RS*)-β-{[1-phenyl-4-(phenylmethylamino)cyclohexyl]methoxy}-3,5-

bis(trifluoromethyl)benzeneethanol (1:1 mixture of *cis*- and *trans*-isomers, Example 45, 140 mg, 0,25 mmol) in methanol (4 mL) and the mixture was shaken under an atmosphere of hydrogen (50 psi) for 16 hours. The mixture was filtered through Celite™ and a slurry of palladium hydroxide (20% , 50 mg) in methanol (10 mL), aqueous formaldehyde (37% , 2 mL) and acetic acid (35 mg) were added. The mixture was shaken under an atmosphere of hydrogen (50 psi) for 16 hours, filtered through Celite™, washing with methanol, and the solvent was evaporated under reduced pressure to give the title compound as an oil (90 mg, 72%). ^{1}H NMR and analytical HPLC showed this to be a 1:2 mixture of *trans*- and *cis*-isomers. m/z (ES^+) 490 (M+1).

EXAMPLE 106

Trans-(*RS*)-β-[(4-Cyclopropylmethylamino-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol Hydrochloride

Prepared from *trans*-(*RS*)-β-[(4-amino-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol (Example 87) and cyclopropane carboxaldehyde according to the method of Example 55. m/z (ES^+) 516 (M+1).

EXAMPLE 107

1,2-Dihydro-5-{[N-(1-{[α-Hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy] methyl}-1-phenylcyclohex-4-yl)methylamino]methyl}-3*H*-1,2,4-triazol-3-one

Methyl 2-(2-chloro-1-iminoethyl)hydrazinecarboxylic acid (*J. Med. Chem.* **1996**, *39*, 2907-2914; 8 mg, 0.05 mmol) was added to a mixture of *trans*-(*RS*)-β-[(4-methylamino-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol (Example 90, 23 mg, 0.04 mmol) and potassium carbonate (30 mg, 0.22 mmol) in dimethylformamide (1 mL) and the mixture was stirred at room temperature for 72 hours. The mixture was poured into water (10 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic fractions were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was dissolved in toluene (10 mL) and the mixture was stirred under reflux for 16 hours. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH/Et_3N (100:0:1 increasing to 90:10:1), to give the title compound as a colorless oil (8 mg, 32%). m/z (ES^+) 573 (M+1).

EXAMPLE 108

Cis-(*RS*)-Methyl 1-(1-{[α-Hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy] methyl}-1-phenylcyclohex-4-yl)piperidine-4-carboxylate and

Trans-(*RS*)-Methyl 1-(1-{[α-Hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy] methyl}-1-phenylcyclohex-4-yl)piperidine-4-carboxylate

A mixture of sodium cyanoborohydride (83 mg, 1.3 mmol) and zinc chloride (90 mg, 0.65 mmol) in methanol (2 mL) was added to a solution of (*RS*)-β-[(4-oxo-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol (Example 15, 300 mg, 0.65 mmol) and ethyl 4-piperidinecarboxylate (307 mg, 1.96 mmol) in methanol (30 mL) and the mixture was stirred at room temperature overnight. The solvent was evaporated under reduced pressure and aqueous sodium hydrogen carbonate (saturated, 3 mL) and dichloromethane (3 mL) were added. The layers were separated and the organic fraction was poured onto an SCX cartridge (Varian Bond Elut™; 10 mL/500 mg). The cartridge was washed with methanol (4 x 2 mL), then eluted with methanolic ammonia (2M, 2 x 2 mL) and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (5 mL) and sodium (catalytic) was added. The mixture was stirred at room temperature for 1 hour, then the solvent was evaporated under reduced pressure and ethyl acetate (50 mL) and water (50 mL) were added. The layers were separated and the organic fraction was dried ($MgSO_4$) and and the solvent was evaporated under reduced pressure. The residue was purified by MPLC chromatography on silica gel, eluting with CH_2Cl_2/MeOH/Et_3N (95:5:0.2) to give:

cis-(RS)-*methyl 1-(1-{[α-hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy]methyl}-1-phenyl cyclohex-4-yl)piperidine-4-carboxylate* as a colorless solid (130 mg, 33%); ^{1}H NMR (360MHz, CD_3OD) δ 1.45-1.94 (10H, m), 2.16-2.36 (6H, m), 2.90-2.95 (2H, m), 3.47 (3H, s), 3.42-3.53 (3H, m), 3.69 (1H, d, *J* 8.8 Hz), 4.30-4.32 (1H, m), 7.22-7.26 (1H, m), 7.32-7.39 (4H, m), 7.56 (2H, s), and 7.78 (1H, s); m/z (ES^+) 588 (M+1); and

trans-(RS)-*methyl 1-(1-{[α-hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy] methyl}-1-phenyl cyclohex-4-yl)piperidine-4-carboxylate* as a colorless solid (97 mg, 25%); ^{1}H NMR (360MHz, CD_3OD) δ 1.27-1.33 (2H, m), 1.60-1.68 (4H, m), 1.77-1.83 (4H, m), 2.12-216 (2H, m), 2.24-2.27 (1H, m), 2.39-2.44 (2H, m), 2.56-2.61 (1H, m), 2.78-2.82 (2H, m), 3.21 (1H, d, *J* 8.8 Hz), 3.33 (1H, d, *J* 8.8 Hz), 3.52 (1H, dd, *J* 11.5, 5.0 Hz), 3.61 (3H, s), 3.58-3.63 (1H, m), 4.31 (1H, t, *J* 5.8 Hz), 7.16-7.20 (1H, m), 7.28-7.33 (2H, m), 7.39-7.41 (2H, m), 7.64 (2H, s), and 7.80 (1H, s); m/z (ES^+) 588 (M+1).

EXAMPLE 109

Trans-(*RS*)-1-(1-{[α-Hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy]methyl}-1-phenylcyclohex-4-yl)piperidine-4-methanol

A solution of diisobutylaluminium hydride (1.0M in toluene, 0.35 mL, 0.35 mmol) was added to a cooled (0 °C) solution of *trans*-(*RS*)-methyl 1-(1-{[α-hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy]methyl}-1-phenyl cyclohex-4-yl)piperidine-4-carboxylate (Example 108, 50 mg, 0.08 mmol) in toluene (5 mL). The solution was allowed to warm to room temperature and stirred for 16 hours. Methanol (2 mL), then water (2 mL) and ethyl acetate (5 mL) were added and the layers were separated. The organic fraction was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound as a colorless solid (40 mg, 84%). m/z (ES^+) 560 (M+1).

EXAMPLE 110

Trans-(*RS*)-1-(1-{[α-Hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy]methyl}-1-phenylcyclohex-4-yl)piperidine-4-carboxylic Acid

Potassium hydroxide (38 mg, 0.68 mmol) was added to a solution of *trans*-(*RS*)-methyl 1-(1-{[α-hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy]methyl}-1-phenyl cyclohex-4-yl)piperidine-4-carboxylate (Example 108, 50 mg, 0.08 mmol) in methanol (5 mL) and the mixture was stirred at room temperature for 16 hours. The solvent was evaporated under reduced pressure and water (2 mL) was added. The mixture was neutralised with hydrochloric acid (2M) and extracted with ethyl acetate (2 x 5 mL). The combined organic fractions were dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound as a colorless solid (28 mg, 56%). m/z (ES^+) 574 (M+1).

EXAMPLE 111

Trans-(*RS*)-1-(1-{[α-Hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy]methyl}-1-phenylcyclohex-4-yl)-α,α-dimethylpiperidine-4-methanol

A solution of *trans*-(*RS*)-methyl 1-(1-{[α-hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy]methyl}-1-phenylcyclohex-4-yl)piperidine-4-carboxylate (Example 108, 21 mg, 0.04 mmol) in tetrahydrofuran (5 mL) was added dropwise to a cooled (0 °C) solution of methyl magnesium bromide (3.0M in ether, 0.05 mL, 0.15 mmol) in tetrahydrofuran (5 mL). The solution was allowed to warm to room temperature and stirred for 4 hours. Aqueous ammonium chloride (saturated, 7 mL), then water (7 mL) and ethyl acetate (10 mL) were added and the layers were separated. The organic fraction was dried

($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound as a colorless solid (13 mg, 62%). m/z (ES^+) 588 (M+1).

EXAMPLE 112

Trans-(*RS*)-1-(1-{[α-Hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy]methyl}-1-phenylcyclohex-4-yl)-N,N-dimethylpiperidine-4-carboxamide

Prepared from *trans*-(*RS*)-1-(1-{[α-hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy]methyl}-1-phenyl cyclohex-4-yl)piperidine-4-carboxylic acid (Example 110) and dimethylamine hydrochloride according to the method of Example 182. m/z (ES^+) 601 (M+1).

EXAMPLE 113

(*RS*)-Methyl (1-(1-{[α-Hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy]methyl}-1-phenylcyclohex-4-ylidene)acetate

Methyl (triphenylphosphoranylidene)acetate (261 mg, 0.78 mmol) was added to a solution of (*RS*)-β-[(4-oxo-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl) benzeneethanol (Example 15, 300 mg, 0.65 mmol) in dichloromethane (5 mL) and the mixture was stirred at 40 °C for 16 hours. Additional methyl (triphenylphosphoranylidene) acetate (217 mg, 0.65 mmol) was added and the mixture was stirred at 40 °C for 16 hours. The mixture was cooled and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with isohexane/EtOAc (80:20), to give the title compound as a colorless oil (290 mg, 86%). ^{1}H NMR (360MHz, $CDCl_3$) δ 1.72-1.86 (3H, m), 2.18-2.29 (3H, m), 2.33-2.56 (2H, m), 3.21 (1H, d, *J* 8.8 Hz), 3.36 (1H, d, *J* 8.8 Hz), 3.49-3.52 (3H, m), 3.67 (3H, s), 4.25-4.32 (1H, m), 5.62 (1H, s), 7.26-7.27 (1H, m), 7.38-7.41 (4H, m), 7.53 (2H, s), and 7.77 (1H, s).

EXAMPLE 114

Cis- and *Trans*-(*RS*)-Methyl (1-(1-{[α-Hydroxymethyl-3,5-bis(trifluoromethyl) phenylmethoxy]methyl}-1-phenylcyclohex-4-yl)acetate

A slurry of palladium on carbon (5%, 10 mg) in methanol (1 mL) was added to a solution of (*RS*)-methyl (1-(1-{[α-hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy] methyl}-1-phenyl cyclohex-4-ylidene)acetate (Example 113, 100 mg, 0.19 mmol) in methanol (5 mL) and the mixture was shaken under an atmosphere of hydrogen (40 psi) for 1 hour. The mixture was filtered through Celite™ and the solvent was evaporated under reduced pressure to give the title compound as an oil (87 mg, 87%). ^{1}H NMR and analytical HPLC showed this to be a

1:1 mixture of *trans*- and *cis*-isomers. ^{1}H NMR (400MHz, $CDCl_3$) δ 1.04-1.35 (2H, m), 1.54-1.87 (6H, m), 2.07-2.50 (3H, m), 3.20-3.29 (2H, m), 3.43-3.51 (2H, m), 3.62 and 3.68 (Total 3H, each s), 4.24-4.32 (1H, m), 7.22-7.43 (5H, m), 7.54 (2H, m), and 7.78 (1H, m).

EXAMPLE 115

Cis-(*RS*)-1-[2-(1-(1-{[α-Hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy] methyl}-1-phenylcyclohex-4-yl)ethyl]pyrrolidine and

Trans-(*RS*)-1-[2-(1-(1-{[α-Hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy] methyl}-1-phenylcyclohex-4-yl)ethyl]pyrrolidine

A solution of diisobutylaluminium hydride (1.0M in hexane, 0.33 mL, 0.33 mmol) was added dropwise to a cooled (-78 °C) solution of (*RS*)-methyl (1-(1-{[α-hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy]methyl}-1-phenyl cyclohex-4-yl)acetate (Example 114, 1:1 mixture of *trans*- and *cis*-isomers, 87 mg, 0.17 mmol) in isohexane/dichloromethane (3:1, 12 mL). The mixture was stirred at -78 °C for 4 hours, then methanol (2 mL), water (2 mL) and ethyl acetate (5 mL) were added. The layers were separated and the organic fraction was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (3 mL) and pyrrolidine (0.14 mL, 1.7 mmol) and a mixture of sodium cyanoborohydride (42 mg, 0.66 mmol) and zinc chloride (46 mg, 0.33 mmol) in methanol (5 mL) were added. The mixture was stirred at room temperature overnight, and the solvent was evaporated under reduced pressure. Aqueous sodium hydrogen carbonate (saturated, 3 mL) and dichloromethane (3 mL) were added and the layers were separated. The organic fraction was poured onto an SCX cartridge (Varian Bond Elut™; 10 mL/500 mg) and the cartridge was washed with methanol (4 x 2 mL), then eluted with methanolic ammonia (2M, 2 x 2 mL). The solvent was evaporated under reduced pressure. The residue was purified by MPLC column chromatography on silica gel, eluting with CH_2Cl_2/MeOH/Et_3N (98:2:0.2) to give:

cis-(RS)-*1-[2-(1-(1-{[α-hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy]methyl}-1-phenyl cyclohex-4-yl)ethyl]pyrrolidine* (13 mg, 14%) as a colorless solid; ^{1}H NMR (360MHz, CD_3OD) δ 1.23-1.45 (3H, m), 1.57-1.74 (6H, m), 2.00-2.08 (4H, m), 2.14-2.20 (1H, m), 2.31-2.35 (1H, m), 3.00-3.22 (6H, m), 3.44-3.60 (3H, m), 3.76 (1H, d, *J* 8.8 Hz), 4.37 (1H, t, *J* 5.6 Hz), 7.14-7.18 (1H, m), 7.24-7.28 (2H, m), 7.37-7.39 (2H, m), 7.65 (2H, s), and 7.81 (1H, s); m/z (ES^+) 544 (M+1); and

trans-(RS)-*1-[2-(1-(1-{[α-hydroxymethyl-3,5-bis(trifluoromethyl)phenylmethoxy] methyl}-1-phenyl cyclohex-4-yl)ethyl]pyrrolidine* (10 mg, 11%) as a colorless solid; ^{1}H NMR (360MHz, CD_3OD) δ 1.01-1.11 (2H, m), 1.46-1.50 (3H, m), 1.60-1.71 (4H, m), 2.01-2.09 (4H, m),

2.36-2.41 (1H, m), 2.51-2.56 (1H, m), 3.03-3.35 (7H, m), 3.35 (1H, d, *J* 8.8 Hz), 3.47 (1H, dd, *J* 10.8, 7.2 Hz), 3.51 (1H, dd, *J* 7.2, 4.3 Hz), 4.31 (1H, t, *J* 5.8 Hz), 7.16-7.20 (1H, m), 7.24-7.31 (2H, m), 7.37-7.40 (2H, m), 7.64 (2H, s), 7.80 (1H, s); m/z (ES^+) 544 (M+1).

EXAMPLE 116

Trans-(*RS*)-Methyl α-({4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl} methoxy)-3,5-bis(trifluoromethyl)benzeneacetate

Methyl α-diazo-3,5-bis(trifluoromethyl)benzeneacetate (WO 95/21819, 97 mg, 0.31 mmol) in dichloromethane (1 mL) was added over 15 minutes to a mixture of *trans*-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanemethanol (Description 21, 98 mg, 0.27 mmol) and rhodium acetate dimer (1 mg) in dichloromethane (1 mL) and the mixture was stirred at room temperature for 1 hour, then at 40 °C for 1 hour. The mixture was cooled and further methyl α-diazo-3,5-bis(trifluoromethyl)benzeneacetate (110 mg, 0.35 mmol) in dichloromethane (1 mL) was added. The mixture was stirred at room temperature for 0.5 hour, then at 40 °C for 0.5 hour. The mixture was cooled, divided into four portions and poured onto four SCX cartridges (Varian Bond Elut™; 10 mL/500 mg). Each cartridge was washed with methanol (4 x 1 mL), then eluted with methanolic ammonia (2M, 4 x 1 mL). The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_3(Aq.) (97.5:2.5:0.25) to give the title compound (61 mg, 35%). m/z (ES^+) 652 (M+1).

EXAMPLE 117

Trans-3,5-Bis(trifluoromethyl)phenylmethyl 4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylate

Prepared from 3,5-bis(trifluoromethyl)phenylmethyl 4-oxo-1-phenylcyclohexanecarboxylate (Example 16) and 4-(4-fluorophenyl)piperidine (Description 16) according to the method of Example 55. The product was purified by preparative thin layer chromatography on silica gel, eluting with CH_2Cl_2/MeOH/Et_3N(Aq.) (95:5:1). m/z (ES^+) 608 (M+1).

EXAMPLE 118

Trans-(*RS*)-1-[3,5-Bis(trifluoromethyl)phenyl]ethyl 4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylate

Oxalyl chloride (31 µl, 0.36 mmol) was added to a mixture of *trans*-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylic acid hydrochloride (Description 20, 50 mg, 0.12 mmol) and dimethylformamide (1 drop) in dichloromethane (2 mL) and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated under

reduced pressure and the residue was dissolved in dichloroethane (2 mL). (*RS*)-α-Methyl-3,5-bis(trifluoromethyl)benzenemethanol (93 mg, 0.36 mmol), triethylamine (59 µl, 0.42 mmol) and 4-dimethylaminopyridine (1 mg) were added and the mixture was stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure and aqueous sodium carbonate (10%, 25 mL) and ethyl acetate (25 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (25 mL). The combined organic fractions were washed with brine (25 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with isohexane/EtOAc (90:10 increasing to 0:100), to give the title compound (39 mg, 52%). m/z (ES^+) 622 (M+1).

EXAMPLE 119

Trans-(*RS*)-2-Hydroxy-2-[3,5-bis(trifluoromethyl)phenyl]ethyl 4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylate

Oxalyl chloride (50 µl) was added to a mixture of *trans*-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylic acid hydrochloride (Description 20, 63 mg, 0.15 mmol) and dimethylformamide (1 drop) in dichloromethane (2 mL) and the mixture was stirred at room temperature for 1 hour. The solvent was evaporated under reduced pressure and the residue was dissolved in dichloroethane (4 mL). Triethylamine (100 µl, 0.72 mmol), (*RS*)-1-[3,5-bis(trifluoromethyl)phenyl]-1,2-ethanediol (Description 3, 110 mg, 0.40 mmol) and 4-dimethylaminopyridine (1 mg) were added and the mixture was stirred at room temperature for 2 hours. Dichloromethane (20 mL) and aqueous sodium carbonate (10%, 20 mL) were added and the layers were separated. The aqueous fraction was extracted with dichloromethane (10 mL), then with ethyl acetate (10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_3(Aq.) (95:5:0.5 increasing to 90:10:1) to give the title compound. m/z (ES^+) 638 (M+1).

EXAMPLE 120

Trans-(*RS*)-α-({[2-(Trimethylsilyl)ethoxy]methoxy}methyl)-[3,5-bis(trifluoromethyl)phenyl]methyl 4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylate

Prepared from *trans*-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylic acid hydrochloride (Description 20) and (*RS*)-1-[3,5-bis(trifluoromethyl)-α-{[2-(trimethylsilyl)ethoxy]methoxymethyl}benzenemethanol (Description 4) according to the method of Example 119. m/z (ES^+) 768 (M+1).

EXAMPLE 121

Trans-(*RS*)-α-(Hydroxymethyl)-[3,5-bis(trifluoromethyl)phenyl]methyl 4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-(phenyl)cyclohexanecarboxylate

Trifluoroacetic acid (0.5 mL) was added to a solution of *trans*-(*RS*)-α-({[2-(trimethylsilyl)ethoxy]methoxy}methyl)-[3,5-bis(trifluoromethyl)phenyl]methyl 4-[4-(4-fluorophenyl)piperidin-1-yl]-1-(phenyl)cyclohexanecarboxylate (Example 120, 37 mg, 48 μmol) in dichloromethane (2 mL) and the mixture was stirred at room temperature for 1 hour. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_3(Aq.) (95:5:0.5) to give the title compound (19 mg, 62%). m/z (ES^+) 638 (M+1).

EXAMPLE 122

Trans-(*RS*)-Methyl α-({4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}carbonyloxy)-3,5-bis(trifluoromethyl)benzeneacetate

Methyl α-diazo-3,5-bis(trifluoromethyl)benzeneacetate (WO 95/21819, 200 mg, 0.64 mmol) in dichloromethane (2 mL) was added to a mixture of *trans*-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylic acid hydrochloride (Description 20, 103 mg, 0.25 mmol) and rhodium acetate dimer (4 mg) in dichloromethane (2 mL) and the mixture was stirred at room temperature for 1 hour. Further methyl α-diazo-3,5-bis(trifluoromethyl)benzeneacetate (100 mg, 0.32 mmol) in dichloromethane (1 mL) was added and the mixture was stirred at room temperature for 1 hour. Further methyl α-diazo-3,5-bis(trifluoromethyl)benzeneacetate (50 mg, 0.16 mmol) in dichloromethane (1 mL) was added and the mixture was stirred at room temperature for 1 hour. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH (97.5:2.5) to give the title compound (18 mg, 11%). m/z (ES^+) 666 (M+1).

EXAMPLE 123

Cis-{4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methyl 3,5-Bis(trifluoromethyl)benzoate and

Trans-{4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methyl 3,5-Bis(trifluoromethyl)benzoate

Sodium triacetoxyborohydride (420 mg, 2 mmol) was added to a mixture of (4-oxo-1-phenylcyclohexyl)methyl 3,5-bis(trifluoromethyl)benzoate (Example 10, 180 mg, 0.4 mmol), 4-(4-fluorophenyl)piperidine (Description 16, 72 mg, 0.4 mmol), and acetic acid (114 μl,

2 mmol) in 1,2-dichloroethane and the mixture was stirred at room temperature for 70 hours. Saturated aqueous sodium hydrogen carbonate (30 mL) was added and the mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic fractions were washed with brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography, eluting with isohexane /EtOAc (50:50) to give:

cis-*{4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methyl 3,5-bis(trifluoromethyl)benzoate* (7.8 mg, 3%); ^{1}H NMR (360MHz, $CDCl_3$) δ 1.69-1.93 (10H, m), 2.24-2.60 (6H, m), 3.15 (2H, br d, *J* 10.6 Hz), 4.60 (2H, s), 6.98 (2H, t, *J* 8.7 Hz), 7.16-7.26 (3H, m), 7.34-7.38 (2H, m), 7.43-7.45 (2H, m), 8.00 (1H, s), and 8.23 (2H, s); m/z (ES^+) 608 (M+1); and

trans-*{4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methyl 3,5-bis(trifluoromethyl)benzoate* (9 mg, 4%); ^{1}H NMR (360MHz, $CDCl_3$) δ 1.34-1.44 (2H, m), 1.60-178 (6H, m), 1.86-1.88 (2H, m), 2.14-2.20 (2H, m), 2.36-2.52 (2H, m), 2.58 (2H, br d, *J* 12.4 Hz), 2.95 (2H, d, *J* 11.4 Hz), 4.23 (2H, s), 6.94 (2H, t, *J* 8.7 Hz), 7.11-7.15 (2H, m), 7.22-7.26 (1H, m), 7.36-7.40 (2H, m), 7.45-7.47 (2H, m), 8.03 (1H, s), and 8.32 (2H, s); m/z (ES^+) 608 (M+1).

EXAMPLE 124

Cis-1-Phenyl-4-(4-phenylpiperidin-1-yl)-N-{[3,5-bis(trifluoromethyl)phenyl]methyl} cyclohexanecarboxamide and

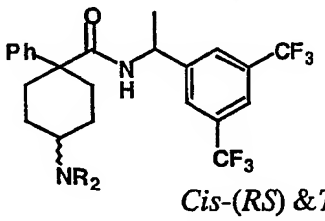
Trans-1-Phenyl-4-(4-phenylpiperidin-1-yl)-N-{[3,5-bis(trifluoromethyl)phenyl]methyl} cyclohexanecarboxamide

Prepared as a mixture of *cis*- and *trans*-isomers from 4-oxo-1-phenyl-N-{[3,5-bis(trifluoromethyl)phenyl]methyl}cyclohexanecarboxamide (Example 17) and 4-phenylpiperidine according to the method of Example 45. The isomers were separated by HPLC purification [YMC R&D CR; isohexane/EtOH (60:40)]:

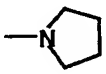
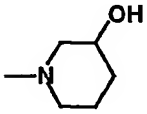
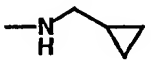
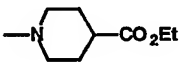
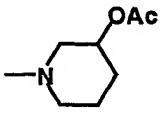
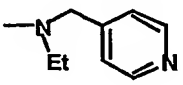
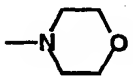
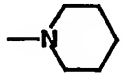
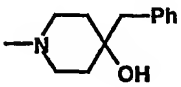
cis-*1-phenyl-4-(4-phenylpiperidin-1-yl)-N-{[3,5-bis(trifluoromethyl)phenyl]methyl} cyclohexanecarboxamide;* ^{1}H NMR (360MHz, CD_3OD) δ 7.79 (1H, s) 7.69 (2H, s), 7.38-7.18 (10H, m), 4.47 (2H, s), 3.15 (2H, m), 3.05-2.40 (6H, m), 2.06 (2H, m), and 1.97-1.78 (9H, m); m/z (ES^+) 589 (M+1);

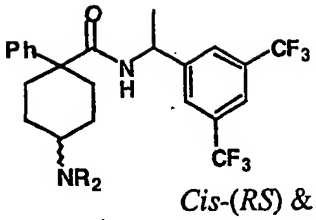
trans-*1-phenyl-4-(4-phenylpiperidin-1-yl)-N-{[3,5-bis(trifluoromethyl)phenyl]methyl} cyclohexanecarboxamide;* ^{1}H NMR (360MHz, CD_3OD) δ 7.74 (1H, s) 7.55 (2H, s), 7.53-7.14 (10H, m), 4.39 (2H, s), 3.06 (2H, m), 2.80 (2H, m), 2.53 (2H, m), 2.32 (2H, m), and 1.99-1.29 (11H, m); m/z (ES^+) 589 (M+1).

The following compounds were prepared as mixtures of *cis*- and *trans*-isomers from (RS)-4-oxo-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl} cyclohexanecarboxamide (Example 18) according to the method of Example 55, substituting a suitable amine for piperidine.

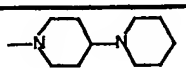
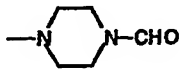
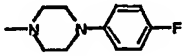
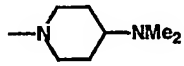
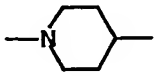
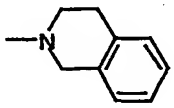
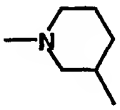
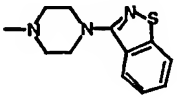
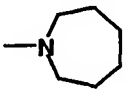
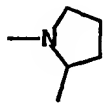
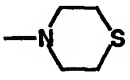
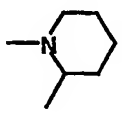


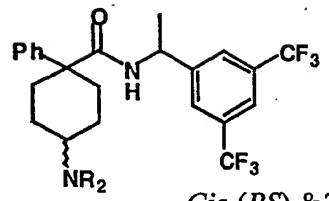
Cis-(*RS*) &*Trans*-(*RS*)

Ex.	-NR_2	Formula	M.W.	m/z (ES^+) (M+1).
125		C24H26F6N2O	472	473
126		C27H30F6N2O	512	513
127		C28H32F6N2O2	542	543
128		C27H30F6N2O	512	513
129		C31H36F6N2O3	598	599
130		C30H34F6N2O3	584	585
131		C31H33F6N3O	577	578
132		C27H30F6N2O2	528	529
133		C28H32F6N2O	526	527
134		C35H38F6N2O2	632	633

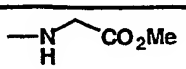
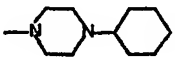
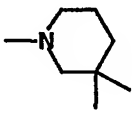
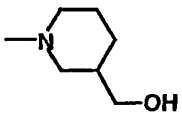
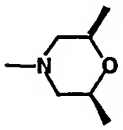
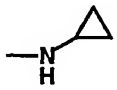


Cis-(RS) &Trans-(RS)

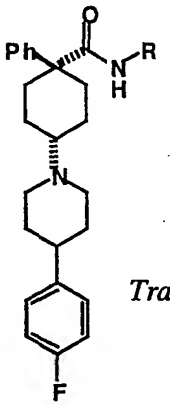
Ex.	-NR_2	Formula	M.W.	m/z (ES^+) (M+1).
135		C33H41F6N3O	609	610
136		C28H31F6N3O2	555	556
137		C33H34F7N3O	621	622
138		C30H37F6N3O	569	570
139		C29H34F6N2O	540	541
140		C32H32F6N2O	574	575
141		C29H34F6N2O	540	541
142		C34H34F6N4OS	660	661
143		C29H34F6N2O	540	541
144		C28H32F6N2O	526	527
145		C27H30F6N2OS	544	545
146		C29H34F6N2O	540	541



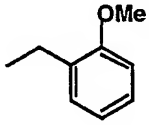
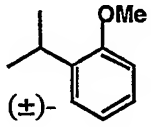
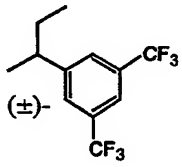
Cis-(*RS*) &*Trans*-(*RS*)

Ex.	-NR_2	Formula	M.W.	m/z (ES^+) (M+1).
147		C26H28F6N2O3	530	531
148		C33H41F6N3O	609	610
149		C30H36F6N2O	554	555
150		C29H34F6N2O2	556	557
151		C29H34F6N2O2	556	557
152		C26H28F6N2O	498	499

The following compounds were prepared from *trans*-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylic acid hydrochloride (Description 20) according to the method of Example 177, substituting a suitable amine for (*RS*)-α-methyl-3,5-bis(trifluoromethyl)benzenemethanamine hydrochloride.



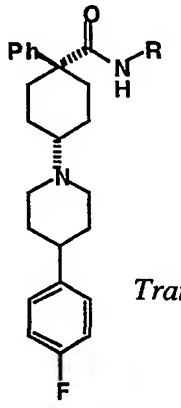
Trans-

Ex.	-R	Formula	M.W.	m/z (ES$^+$) (M+1).
153		C32H37FN2O2	500	501
154[1]		C33H39FN2O2	514	515
155[2]		C35H37F7N2O	634	635

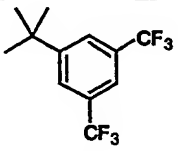
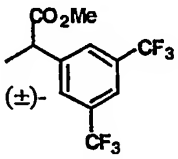
[1] (*RS*)-2-Methoxy-α-methylbenzenemethanamine Hydrochloride: Description 6.

[2] (*RS*)-α-Ethyl-3,5-bis(trifluoromethyl)benzenemethanamine Hydrochloride: Description 7.

The following compounds were prepared from *trans*-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylic acid hydrochloride (Description 20) according to the method of Example 158, substituting a suitable amine for 3-(methoxy)benzenemethanamine.



Trans-

Ex.	-R	Formula	M.W.	m/z (ES$^+$) (M+1).
156[1]		C35H37F7N2O	634	635
157[2]		C35H35F7N2O3	664	665

[1] α,α-Dimethyl-3,5-bis(trifluoromethyl)benzenemethanamine Hydrochloride: Description 11.

[2] (*RS*)-Methyl α-Amino-3,5-bis(trifluoromethyl)benzeneacetate Hydrochloride: Description 12.

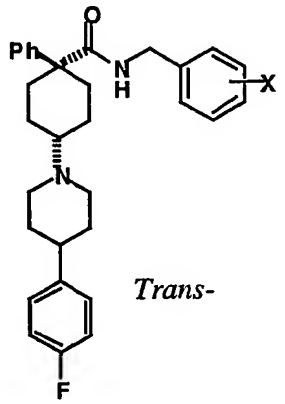
EXAMPLE 158

Trans-4-[4-(4-Fluorophenyl)piperidin-1-yl]-N-{[3-(methoxy)phenyl]methyl}-1-phenylcyclohexanecarboxamide

Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (40 mg, 0.16 mmol) was added to a solution of *trans*-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylic acid hydrochloride (Description 20, 50 mg, 0.13 mmol) and triethylamine (91 µl, 0.65 mmol) in dichloromethane

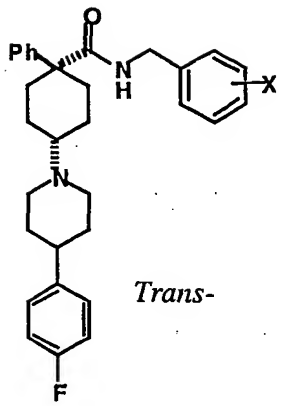
(5 mL) and the mixture was stirred at room temperature for 10 minutes. 3-(Methoxy)benzenemethanamine (18 µl, 0.14 mmol) was added and the mixture was stirred at room temperature overnight. Aqueous sodium carbonate (10%, 20 mL) and ethyl acetate (20 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate(2 x 20 mL) and the combined organic fractions were washed with brine (20 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (0.5 mL) and poured onto an SCX cartridge (Varian Bond Elut™; 10 mL/500 mg). The cartridge was washed with methanol (2 x 5 mL), then eluted with methanolic ammonia (2M, 5 mL). The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_3(Aq.) (96:4:0.4), to give the title compound (38 mg, 58%).
m/z (ES^+) 501 (M+1).

The following compounds were prepared from *trans*-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylic acid (Description 20) according to the method of Example 158, substituting a suitable amine for 3-(methoxy)benzenemethanamine.



Trans-

Ex.	-X-	Formula	M.W.	m/z (ES^+) (M+1).
159	2-Cl	C31H34ClFN2O	504	505
			506	507
160	3-Cl	C31H34ClFN2O	504	505
			506	507
161	2,3-Cl_2	C31H33Cl2FN2O	538	539
			540	541
			542	543



Trans-

Ex.	-X-	Formula	M.W.	m/z (ES$^+$) (M+1).
162	2,4-Cl_2	C31H33Cl2FN2O	538	539
			540	541
			542	543
163	3-Cl-4-F	C31H33ClF2N2O	522	523
			524	525
164	2,4-F_2	C31H33F3N2O	506	507
165	2,6-F_2	C31H33F3N2O	506	507
166	3,5-F_2	C31H33F3N2O	506	507
167	2,3-Me_2	C33H39FN2O	498	499
168	2-CF_3	C32H34F4N2O	538	539
169	3-CF_3	C32H34F4N2O	538	539
170	4-CF_3	C32H34F4N2O	538	539
171	2,4-$(OMe)_2$	C33H39FN2O3	530	531
172	3,5-$(OMe)_2$	C33H39FN2O3	530	531
173	2,4,6-$(OMe)_3$	C34H41FN2O4	560	561
174	2,6-$(OMe)_2$	C33H39FN2O3	530	531
175	3,4-$(OMe)_2$	C33H39FN2O3	530	531
176	2,5-$(OMe)_2$	C33H39FN2O3	530	531

EXAMPLE 177

Trans-(*RS*)-4-[4-(4-Fluorophenyl)piperidin-1-yl]-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide

Triethylamine (0.13 mL, 0.96 mmol) was added to a mixture of *trans*-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylic acid hydrochloride (Description 20, 100 mg, 0.24 mmol), (*RS*)-α-methyl-3,5-bis(trifluoromethyl) benzenemethanamine hydrochloride (Description 5, 125 mg, 0.43 mmol) and 1-hydroxy benzotriazole (129 mg, 0.96 mmol) in dimethylformamide (10 mL) and the mixture was stirred at room temperature for 10 minutes. 1-(Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (184 mg, 0.96 mmol) was added and the mixture was stirred at room temperature for 24 hours. The mixture was poured into water and extracted with ethyl acetate. The combined organic fractions were washed with aqueous sodium carbonate (saturated), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_3(Aq.) (90:10:1) to give the title compound as a colorless solid (145 mg, 97%). m/z (ES^+) 621 (M+1).

EXAMPLE 178

Trans-(*R*)-4-[4-(4-Fluorophenyl)piperidin-1-yl]-N-{1-[3,5-bis(trifluoromethyl)phenyl] ethyl}-1-phenylcyclohexanecarboxamide and

Trans-(*S*)-4-[4-(4-Fluorophenyl)piperidin-1-yl]-N-{1-[3,5-bis(trifluoromethyl)phenyl] ethyl}-1-phenylcyclohexanecarboxamide

The mixture of enantiomers of Example 177 was separated by chiral HPLC (Chirobiotic V; MeOH/Et_3N/AcOH; 100:0.1:0.1; 1 mL/min; 260 nm) to give:

trans-(R)-*4-[4-(4-fluorophenyl)piperidin-1-yl]-N-{1-[3,5-bis(trifluoromethyl)phenyl] ethyl}-1-phenylcyclohexanecarboxamide*; m/z (ES^+) 621 (M+1); and

trans-(S)-*4-[4-(4-fluorophenyl)piperidin-1-yl]-N-{1-[3,5-bis(trifluoromethyl)phenyl] ethyl}-1-phenylcyclohexanecarboxamide*; m/z (ES^+) 621 (M+1).

EXAMPLE 179

Cis-(*RS*)-4-[4-(4-Fluorophenyl)piperidin-1-yl]-N-{1-[3,5-bis(trifluoromethyl)phenyl] ethyl}-1-phenylcyclohexanecarboxamide Hydrochloride

Prepared from *cis*-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylic acid (Description 19) and (*RS*)-α-methyl-3,5-bis(trifluoromethyl)benzenemethanamine hydrochloride (Description 5) according to the method of Example 177. m/z (ES^+) 621 (M+1).

EXAMPLE 180

Trans-N-Methyl-1-phenyl-4-(4-phenylpiperidin-1-yl)-N-{[3,5-bis(trifluoromethyl)phenyl]methyl}cyclohexanecarboxamide

Prepared from 1-phenyl-4-(4-phenylpiperidin-1-yl)-N-{[3,5-bis(trifluoromethyl)phenyl] methyl}cyclohexanecarboxamide (Mixture of *cis*- and *trans*-isomers, Example 124) according to the method of Example 156, followed by HPLC purification [YMC R&D CR; isohexane/EtOH (60:40)]. m/z (ES^+) 603 (M+1).

EXAMPLE 181

Trans-(*RS*)-4-[4-(4-Fluorophenyl)piperidin-1-yl]-N-methyl-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide

Sodium hydride (60% in mineral oil, 6.5 mg, 0.16 mmol) was added to a solution of *trans*-(*RS*)-4-[4-(4-fluorophenyl)piperidin-1-yl]-N-{1-[3,5-bis(trifluoromethyl)phenyl] ethyl}-1-phenylcyclohexanecarboxamide (Example 177, 50 mg, 0.08 mmol) in dimethylformamide (5 mL) and the mixture was stirred at room temperature for 30 minutes. Iodomethane (15 µl, 0.24 mmol) was added and the mixture was stirred for 1 hour. Aqueous ammonium chloride (saturated) was added and the mixture was extracted with ethyl acetate. The combined organic fractions were washed with water, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC (Hichrom RPB; 250 x 20 mm; 65%MeCN in 0.1%TFA-H_2O; 20 mL/min; 210 nm) to give the title compound as a colorless solid, (20 mg, 39%). m/z (ES^+) 635 (M+1).

EXAMPLE 182

Trans-(*RS*)-4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenyl-N-{2-hydroxy-1-[3,5-bis(trifluoromethyl)phenyl]}ethyl}cyclohexanecarboxamide

Lithium borohydride (12 mg, 0.55 mmol) was added to a solution of *trans*-(*RS*)-methyl α-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}carbonylamino)-3,5-bis(trifluoromethyl)benzeneacetate (Example 157, 100 mg, 0.15 mmol) in tetrahydrofuran (4 mL) and the mixture was stirred at room temperature for 1.5 hours. Hydrochloric acid (2M, 1 mL) was added and the mixture was stirred at room temperature for 10 minutes. Potassium carbonate (500 mg) was added and the mixture was extracted with ethyl acetate (2 x 30 mL). The combined organic fractions were washed with aqueous sodium carbonate (10%, 20 mL) and brine (20 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_3(Aq.) (95:5:0.5) to give the title compound (41 mg, 43%). m/z (ES^+) 637 (M+1).

EXAMPLE 183

Trans-(*RS*)-4-(1,4-Dioxa-8-azaspiro[4.5]decane-8-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide

Sodium triacetoxyborohydride (303 mg, 1.4 mmol) was added to a degassed solution of 4-oxo-1-phenylcyclohexanecarboxylic acid (Description 2, 260 mg, 1.2 mmol) and 1,4-dioxa-8-azaspiro[4.5]decane (0.15 mL, 168 mg, 1.2 mmol) in dichloroethane (5 mL) and the mixture was stirred at room temperature for 20 hours. The solvent was evaporated under reduced pressure and the residue was suspended in dichloromethane. Triethylamine (0.83 mL, 0.60 g, 6 mmol) and bis(2-oxo-3-oxazolidinyl)phosphonic chloride (460 mg, 1.8 mmol) were added. The mixture was stirred at room temperature for 10 minutes, then (*RS*)-α-methyl-3,5-bis(trifluoromethyl)benzenemethanamine hydrochloride(Description 5, 420 mg, 1.4 mmol) was added and the mixture was stirred at room temperature for 20 hours. Aqueous sodium carbonate was added and the mixture was extracted with dichloromethane. The combined organic fractions were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_3(Aq.) (96:4:0.4) to give the title compound (120 mg, 17%).
m/z (ES^+) 585 (M+1).

EXAMPLE 184

Trans-(*RS*)-4-(4-Oxopiperidin-1-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide

Prepared from *trans*-4-(4-oxopiperidin-1-yl)-1-phenylcyclohexanecarboxylic acid hydrochloride (Description 24) and (*RS*)-α-methyl-3,5-bis(trifluoromethyl) benzenemethanamine hydrochloride (Description 5) according to the method of Example 158.
m/z (ES^+) 541 (M+1).

EXAMPLE 185

Trans-(*RS*)-4-(4-Hydroxypiperidin-1-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide

Sodium borohydride (22.5 mg, 0.59 mmol) was added to a solution of *trans*-(*RS*)-4-(4-oxopiperidin-1-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl} cyclohexanecarboxamide (Example 184, 319 mg, 0.59 mmol) in ethanol (3 mL) and the mixture was stirred at room temperature for 1 hour. Aqueous ammonium chloride (saturated, 1 mL) and aqueous sodium carbonate (saturated, 10 mL) were added and the mixture was extracted with ethyl acetate (2 x 15 mL). The combined organic fractions were dried (Na_2SO_4)

and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_3(Aq.) (95:5:0.5 increasing to 85:15:1.5) to give the title compound (250 mg, 78%). m/z (ES^+) 543 (M+1).

EXAMPLE 186

Trans-(*RS*)-4-(But-3-enylamino)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl} cyclohexanecarboxamide

(N-Ethylethanaminato)trifluorosulfur (45 µl, 59 mg, 0.36 mmol) was added dropwise to a cooled (-60 °C) solution of *trans*-(*RS*)-4-(4-hydroxypiperidin-1-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide (Example 185, 90 mg, 0.16 mmol) in ethyl acetate (5 mL) and the mixture was stirred at -60 °C for 1 hour, then allowed to warm to room temperature. Aqueous sodium hydrogen carbonate (saturated, 10 mL) was added and the mixture was extracted with ethyl acetate (2 x 20 mL). The combined organic fractions were washed with aqueous sodium carbonate (saturated, 20 mL) and brine (20 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by MPLC chromatography on silica gel, eluting with EtOAc/MeOH (85:15) to give the title compound (45 mg, 53%). m/z (ES^+) 513 (M+1).

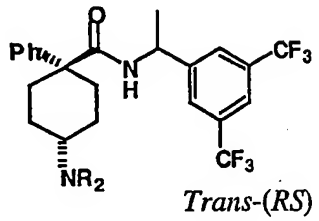
EXAMPLE 187

Trans-(*RS*)-4-(4-Hydroxy-4-phenylpiperidin-1-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide

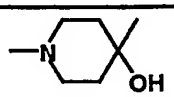
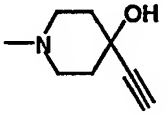
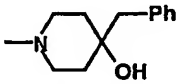
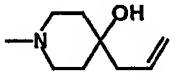
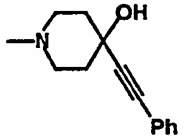
Phenylmagnesium bromide (1M in tetrahydrofuran, 0.3 mL, 0.3 mmol) was added dropwise to a cooled (0 °C) solution of *trans*-(*RS*)-4-(4-oxopiperidin-1-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide (Example 184, 53 mg, 0.1 mmol) in tetrahydrofuran (2 mL) and the mixture was stirred at 0 °C for 10 minutes, then at room temperature for 1 hour. Aqueous ammonium chloride (saturated, 0.3 mL) and aqueous sodium carbonate (saturated, 10 mL) were added and the mixture was extracted with ethyl acetate (2 x 10 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (1 mL) and poured onto an SCX cartridge (Varian Bond Elut™; 10 mL/500 mg). The cartridge was washed with methanol (4 x 1 mL), then eluted with methanolic ammonia (2M, 4 x 1 mL). The solvent was evaporated under reduced pressure to give the title compound (45 mg, 75%).
m/z (ES^+) 619 (M+1).

The following compounds were prepared from *trans*-(*RS*)-4-(4-oxopiperidin-1-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide (Example 184)

according to the method of Example 187, substituting a suitable Grignard reagent for phenylmagnesium bromide.



Trans-(*RS*)

Ex.	-NR_2	Formula	M.W.	m/z (ES^+) (M+1).
188		C29H34F6N2O2	556	557
189		C30H32F6N2O2	566	567
190		C35H38F6N2O2	632	633
191		C31H36F6N2O2	582	583
192		C36H36F6N2O2	642	643

EXAMPLE 193

Trans-(*RS*)-4-(1,2,3,6-Tetrahydro-4-phenylpyridin-1-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide

p-Toluenesulfonic acid hydrate (10 mg, 0.05 mmol) was added to a solution of *trans*-(*RS*)-4-(4-hydroxy-4-phenylpiperidin-1-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide (Example 187, 26 mg, 0.04 mmol) in toluene (8 mL) and the mixture was heated under reflux for 8 hours. The mixture was cooled and aqueous sodium carbonate (saturated, 20 mL) was added. The mixture was extracted with ethyl acetate (2 x 20 mL) and the combined organic fractions were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (1 mL) and poured onto an SCX cartridge (Varian Bond Elut™; 10 mL/500 mg). The cartridge was washed with methanol (4 x 1 mL), then eluted with methanolic ammonia

(2M, 4 x 1 mL). The solvent was evaporated under reduced pressure to give the title compound (24 mg, 94%). m/z (ES^+) 601 (M+1).

EXAMPLE 194

Trans-(*RS*)-4-(1,2,3,6-Tetrahydro-4-methylpyridin-1-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide

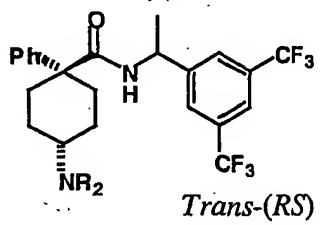
Prepared from *trans*-(*RS*)-4-(4-hydroxy-4-methylpiperidin-1-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide (Example 188) according to the method of Example 193. m/z (ES^+) 539 (M+1).

EXAMPLE 195

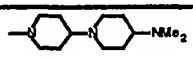
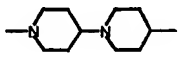
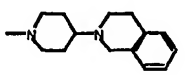
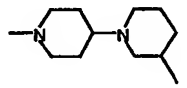
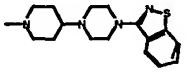
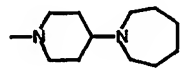
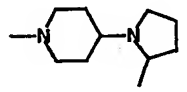
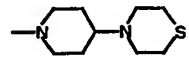
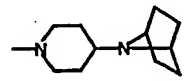
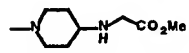
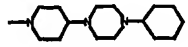
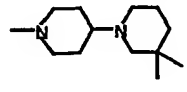
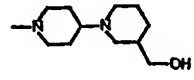
Trans-(*RS*)-4-(4-Hydroxy-4-(phenylethyl)piperidin-1-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide

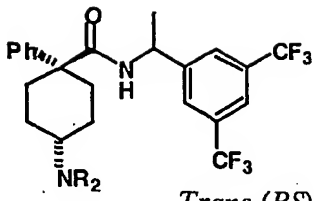
Palladium on carbon (5%, 5 mg) was added to a solution of *trans*-(*RS*)-4-(4-hydroxy-4-(phenylethynyl)piperidin-1-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl} cyclohexanecarboxamide (Example 192, 23 mg, 0.036 mmol) in ethanol (10 mL) and hydrochloric acid (2M, 1 mL) and the mixture was shaken under an atmosphere of hydrogen (50 psi) for 24 hours. The mixture was filtered through Celite™ and the solvent was evaporated under reduced pressure. Ethyl acetate (10 mL) and aqueous sodium carbonate (10%, 10 mL) were added and the layers were separated. The aqueous fraction was extracted with ethyl acetate (10 mL) and the combined organic fractions were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (1 mL) and poured onto an SCX cartridge (Varian Bond Elut™; 10 mL/500 mg). The cartridge was washed with methanol (4 x 1 mL), then eluted with methanolic ammonia (2M, 4 x 1 mL). The solvent was evaporated under reduced pressure to give the title compound (20 mg, 86%). m/z (ES^+) 647 (M+1).

The following compounds were prepared from *trans*-(*RS*)-4-(4-oxopiperidin-1-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl) phenyl]ethyl}cyclohexanecarboxamide (Example 184) according to the method of Example 55, substituting a suitable amine for piperidine.

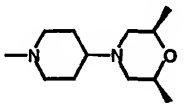
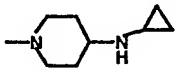


Trans-(*RS*)

Ex.	-NR_2	Formula	M.W.	m/z (ES^+) (M+1).
196		C35H46F6N4O	652	653
197		C34H43F6N3O	623	624
198		C37H41F6N3O	657	658
199		C34H43F6N3O	623	624
200		C39H43F6N5OS	743	744
201		C34H43F6N3O	623	624
202		C33H41F6N3O	609	610
203		C32H39F6N3OS	627	628
204		C34H41F6N3O	621	622
205		C31H37F6N3O3	613	614
206		C38H50F6N4O	692	693
207		C35H45F6N3O	637	638
208		C34H43F6N3O2	639	640



Trans-(RS)

Ex.	-NR_2	Formula	M.W.	m/z (ES^+) (M+1).
209		C34H43F6N3O2	639	640
210		C31H37F6N3O	581	582

EXAMPLE 211

Cis-(RS)-4-[(Phenylmethyl)amino]-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide and

Trans-(RS)-4-[(Phenylmethyl)amino]-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide

Prepared from (*RS*)-4-oxo-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl} cyclohexanecarboxamide (Example 18) and benzylamine according to the method of Example 45:

Cis-(RS)-*4-[(phenylmethyl)amino]-N-{1-[3,5-bis(trifluoromethyl) phenyl]ethyl}-1-phenylcyclohexanecarboxamide* ; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.70 (1H, s), 7.46 (2H, s), 7.33-7.24 (10H, m), 5.09 (1H, q, *J* 7.0 Hz), 3.83 (2H, s), 2.58-2.55 (2H, m), 2.43 (1H, br d, *J* 15.2 Hz), 2.04 (1H, br d, *J* 11.4 Hz), 1.95-1.87 (2H, m), 1.64-1.42 (3H, m), and 1.37 (3H, d, *J* 7.0 Hz); m/z (ES^+) 549 (M+1);

Trans-(RS)-*4-[(phenylmethyl)amino]-N-{1-[3,5-bis(trifluoromethyl) phenyl]ethyl}-1-phenylcyclohexanecarboxamide* ; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.50-7.42 (6H, m), 7.34-7.21 (6H, m), 5.00 (1H, q, *J* 7.0 Hz), 3.75 (2H, s), 2.72-2.67 (1H, m), 2.48 (1H, br d, *J* 14.3 Hz), 2.37 (1H, br d, *J* 14.2 Hz), 2.17-2.06 (2H, m), 1.92-1.88 (2H, m), 1.39-1.16 (2H, m), and 1.27 (3H, d, *J* 7.0 Hz); m/z (ES^+) 549 (M+1).

EXAMPLE 212

Trans-(*RS*)-4-[N-Methyl(phenylmethyl)amino]-N-{1-[3,5-bis(trifluoromethyl)phenyl] ethyl}-1-phenylcyclohexanecarboxamide

Sodium cyanoborohydride (275 mg, 4.38 mmol) was added to a solution of *trans*-(*RS*)-4-[(phenylmethyl)amino]-N-{1-[3,5-bis(trifluoromethyl) phenyl]ethyl}-1-phenylcyclohexanecarboxamide (Example 211, 1.2 g, 2.19 mmol) and aqueous formaldehyde (37% , 820 µl, 10.94 mmol) in acetonitrile (20 mL) and the mixture was stirred at room temperature for 15 minutes. Acetic acid was added until the pH was neutral. The mixture was stirred at room temperature for 45 minutes, adding further acetic acid to maintain neutral pH. The solvent was evaporated under reduced pressure and aqueous sodium hydroxide (1M, 20 mL) and dichloromethane (20 mL) were added. The layers were separated and the aqueous layer was extracted dichloromethane (2 x 20 mL). The combined organic fractions were washed with brine (40 mL), dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give the title compound (1.26 g, 100%). m/z (ES^+) 563 (M+1).

EXAMPLE 213

Trans-(*RS*)-4-Methylamino-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide

Prepared from *trans*-(*RS*)-4-[N-methyl(phenylmethyl)amino]-N-{1-[3,5-bis(trifluoromethyl) phenyl]ethyl}-1-phenylcyclohexanecarboxamide (Example 212) according to the method of Example 229. m/z (ES^+) 473 (M+1).

EXAMPLE 214

Trans-(*RS*)-4-Amino-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide

Triphenylphosphine (1.0 g, 3.82 mmol) was added to a solution of *trans*-(*RS*)-4-azido-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide (Description 28, 920 mg, 1.90 mmol) in tetrahydrofuran (10 mL) and water (1 mL) and the mixture was heated under reflux for 24 hours. The mixture was cooled and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_3(Aq.) (80:20:2), to give the title compound as a colorless solid (670 mg, 87%). m/z (ES^+) 459 (M+1), 442 (M+1-NH_3).

EXAMPLE 215

Trans-(*RS*)-4-(Dimethylamino)-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide

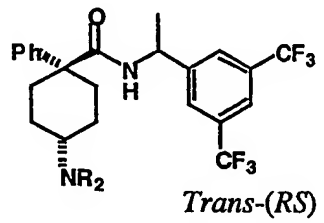
Palladium hydroxide (50 mg) was added to a solution of *trans*-(*RS*)-4-amino-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide (Example 214, 50 mg, 0.11 mmol) and aqueous formaldehyde (37%, 2 mL) in methanol (10 mL) and the mixture was shaken under an atmosphere of hydrogen (50 psi) for 18 hours. The mixture was filtered through a glass fibre pad, washing with methanol, and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate, washed with aqueous sodium carbonate (saturated), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was dissolved in ethanol and ethereal hydrogen chloride (1M) was added. The solvent was evaporated under reduced pressure and the residue was crystallised from EtOAc/Et_2O (50:50) to give the title compound as a colorless solid (20 mg, 35%).
m/z (ES^+) 487 (M+1).

EXAMPLE 216

Trans-(*RS*)-4-[4-(Phenylbutyl)amino]-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide Hydrochloride

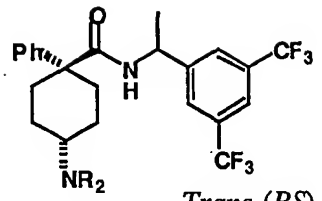
Prepared from *trans*-(*RS*)-4-amino-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide (Example 214) and benzenebutanal (Description 17) according to the method of Example 55. m/z (ES^+) 591 (M+1).

The following compounds were prepared from *trans*-(*RS*)-4-amino-N-{1-[3,5-bis(trifluoromethyl) phenyl]ethyl}-1-phenylcyclohexanecarboxamide (Example 214) according to the method of Example 45, substituting a suitable aldehyde or ketone for benzylamine.

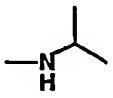
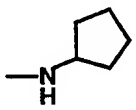
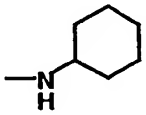
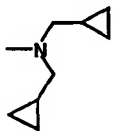
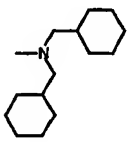
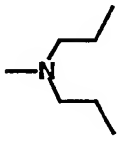
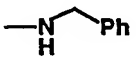


Trans-(*RS*)

Ex.	-NR_2	Formula	M.W.	m/z (ES^+) (M+1).



Trans-(*RS*)

Ex.	-NR_2	Formula	M.W.	m/z (ES^+) (M+1).
217		C26H30F6N2O	500	501
218		C28H32F6N2O	526	527
219		C29H34F6N2O	540	541
220		C31H36F6N2O	566	567
221		C37H48F6N2O	650	651
222		C29H36F6N2O	542	543
223		C30H30F6N2O	548	549

EXAMPLE 224

Trans-(*RS*)-4-[N-Methyl-4-(phenylbutyl)amino]-N-{1-[3,5-bis(trifluoromethyl)phenyl] ethyl}-1-phenylcyclohexanecarboxamide

Prepared from *trans*-(*RS*)-4-[4-(phenylbutyl)amino]-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide Hydrochloride (Example 216) according to the method of Example 215. m/z (ES^+) 605 (M+1).

EXAMPLE 225

Trans-(*RS*)-4-Acetylamino-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide

Acetic anhydride (0.1 mL, 1.1 mmol) was added to a solution of *trans*-(*RS*)-4-amino-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide (Example 214, 50 mg, 0.11 mmol) in dichloromethane (5 mL) and the mixture was stirred at room temperature overnight. The mixture was diluted with dichloromethane (50 mL) and washed with aqueous sodium carbonate (saturated) and water, dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give the title compound as a colorless foam, (54 mg, 98%). m/z (ES^+) 501 (M+1).

EXAMPLE 226

Trans-(*RS*)-4-[(1-Oxo-4-phenylbutyl)amino]-N-{1-[3,5-bis(trifluoromethyl)phenyl] ethyl}-1-phenylcyclohexanecarboxamide

Prepared from *trans*-(*RS*)-4-amino-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide (Example 214) and benzenebutanoic acid (27 mg, 0.16 mmol) according to the method of Example 158. m/z (ES^+) 605 (M+1).

EXAMPLE 227

Cis- and *Trans*-(*RS*)-1,1-Dimethylethyl 4-[1-({1-[3,5-Bis(trifluoromethyl)phenyl] ethylamino}carbonyl)-1-phenylcyclohex-4-yl]-1-piperazinecarboxylate

Prepared as a mixture of *cis*- and *trans*-isomers from (*RS*)-4-oxo-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide (Example 18) and 1,1-dimethylethyl 1-piperazinecarboxylate according to the method of Example 45. m/z (ES^+) 628 (M+1).

EXAMPLE 228

Trans-(*RS*)-4-[4-(Phenylmethyl)piperazin-1-yl]-N-{1-[3,5-bis(trifluoromethyl)phenyl] ethyl}-1-phenylcyclohexanecarboxamide

Bis(2-oxo-3-oxazolidinyl)phosphinic chloride (1.56 g, 6.12 mmol) was added to a mixture of *trans*-4-[4-(phenylmethyl)piperazin-1-yl]-1-phenylcyclohexanecarboxylic acid hydrochloride (Description 25, 1.92 g, 5.1 mmol) and triethylamine (3.55 mL, 25.5 mmol) in dichloromethane (200 mL) and the mixture was stirred at room temperature for 15 minutes. (*RS*)-α-Methyl-3,5-bis(trifluoromethyl)benzenemethanamine hydrochloride (Description 5, 1.64 g, 5.6 mmol) was added and the mixture was stirred at room temperature for 3 days. The solvent was evaporated under reduced pressure and aqueous sodium carbonate (10%, 100 mL)

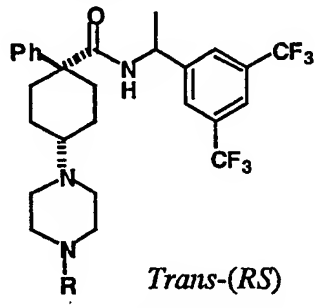
and ethyl acetate (100 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate(100 mL). The combined organic fractions were washed with aqueous sodium carbonate (10%, 100 mL) and brine (20 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (25 mL) and ethereal hydrogen chloride (1M, 10.2 mL) was added. The solid was collected and aqueous sodium carbonate (10%, 100 mL) and ethyl acetate (100 mL) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (100 mL). The combined organic fractions were washed with aqueous sodium carbonate (10%, 100 mL) and brine (20 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound (1.7 g, 54%). m/z (ES^+) 618 (M+1).

EXAMPLE 229

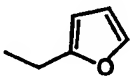
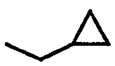
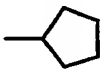
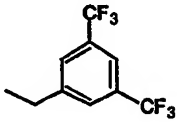
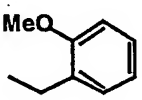
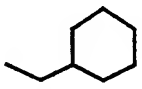
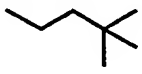
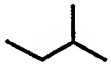
Trans-(*RS*)-4-(Piperazin-1-yl)-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide

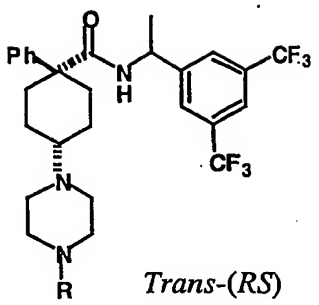
Palladium hydroxide on carbon (20%, 20 mg) was added to a mixture of *trans*-(*RS*)-4-[4-(phenylmethyl)piperazin-1-yl]-N-{1-[3,5-bis(trifluoromethyl) phenyl]ethyl}-1-phenylcyclohexanecarboxamide (Example 228, 700 mg, 1.3 mmol), hydrochloric acid (1M, 2.6 mL) and acetic acid (5 mL) in ethyl acetate (50 mL) and the mixture was shaken under an atmosphere of hydrogen (50psi) for 20 hours. The mixture was filtered through a glass fibre pad, washing with ethyl acetate, and the solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane (20 mL) and washed with aqueous sodium carbonate (10%, 20 mL) and brine (20 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_3(Aq.) (90:10:1), to give the title compound. m/z (ES^+) 528 (M+1).

The following compounds were prepared from *trans*-(*RS*)-4-(piperazin-1-yl)-N-{1-[3,5-bis(trifluoromethyl) phenyl]ethyl}-1-phenylcyclohexanecarboxamide (Example 229) according to the method of Example 45, substituting a suitable aldehyde or ketone for (*RS*)-β-[(4-oxo-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol.

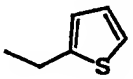
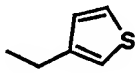
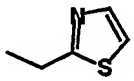
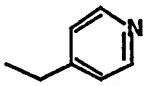
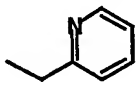
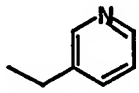


Trans-(*RS*)

Ex.	-R	Formula	M.W.	m/z (ES+) (M+1).
230		C32H35F6N3O2	607	608
231		C31H37F6N3O	581	582
232		C30H37F6N3O	569	570
233		C32H39F6N3O	595	596
234		C36H35F12N3O	753	754
235		C35H39F6N3O2	647	648
236		C34H43F6N3O	623	624
237		C33H43F6N3O	611	612
238		C31H39F6N3O	583	584



Trans-(*RS*)

Ex.	-R	Formula	M.W.	m/z (ES⁺) (M+1).
239		C32H35F6N3OS	623	624
240		C32H35F6N3OS	623	624
241		C35H39F6N3O	631	632
242		C31H34F6N4OS	624	625
243		C33H36F6N4O	618	619
244		C33H36F6N4O	618	619
245		C33H36F6N4O	618	619

EXAMPLE 246

Trans-(*RS*)-4-(4-Methylpiperazin-1-yl)-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide

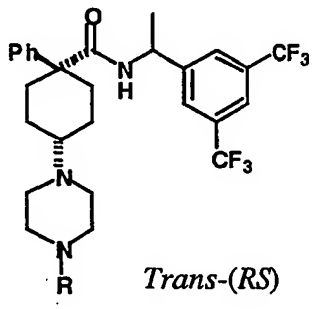
Prepared from *trans*-(*RS*)-4-(piperazin-1-yl)-N-{1-[3,5-bis(trifluoromethyl) phenyl]ethyl}-1-phenylcyclohexanecarboxamide (Example 229) according to the method of Example 215. m/z (ES⁺) 542 (M+1).

EXAMPLE 247

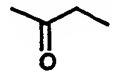
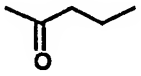
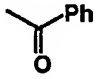
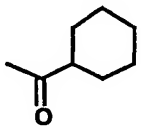
Trans-(*RS*)-4-(4-Acetylpiperazin-1-yl)-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide

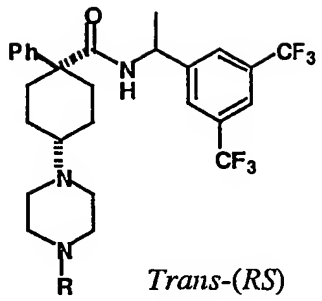
Acetyl chloride (100 µl) was added to a solution of *trans*-(*RS*)-4-(piperazin-1-yl)-N-{1-[3,5-bis(trifluoromethyl) phenyl]ethyl}-1-phenylcyclohexanecarboxamide (Example 229, 25 mg, 0.05 mmol) in dichloromethane (3 mL) and the mixture was stirred at room temperature for 20 minutes. The solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (20 mL). The mixture was washed with aqueous sodium carbonate (10%, 20 mL) and brine (20 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give the title compound (27 mg, 95%). m/z (ES^+) 570 (M+1).

The following compounds were prepared from *trans*-(*RS*)-4-(piperazin-1-yl)-N-{1-[3,5-bis(trifluoromethyl) phenyl]ethyl}-1-phenylcyclohexanecarboxamide (Example 229) according to the method of Example 247, substituting a suitable acid chloride for acetyl chloride.

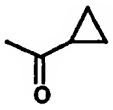
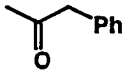


Trans-(*RS*)

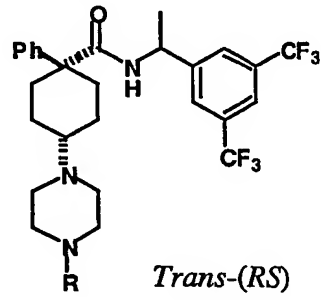
Ex.	-R	Formula	M.W.	m/z (ES^+) (M+1).
248		C30H35F6N3O2	583	584
249		C31H37F6N3O2	597	598
250		C34H35F6N3O2	631	632
251		C34H41F6N3O2	637	638



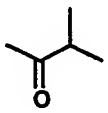
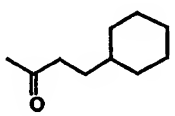
Trans-(*RS*)

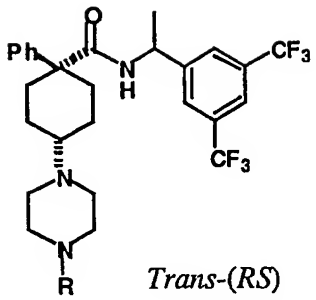
Ex.	-R	Formula	M.W.	m/z (ES⁺) (M+1).
252		C31H35F6N3O2	595	596
253		C35H37F6N3O2	645	646

The following compounds were prepared from *trans*-(*RS*)-4-(piperazin-1-yl)-N-{1-[3,5-bis(trifluoromethyl) phenyl]ethyl}-1-phenylcyclohexanecarboxamide (Example 229) according to the method of Example 158, substituting a suitable acid for *trans*-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarboxylic acid hydrochloride.

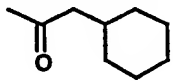
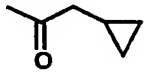


Trans-(*RS*)

Ex.	-R	Formula	M.W.	m/z (ES⁺) (M+1).
254		C31H37F6N3O2	597	598
255		C36H45F6N3O2	665	666



Trans-(*RS*)

Ex.	-R	Formula	M.W.	m/z (ES$^+$) (M+1).
256		C35H43F6N3O2	651	652
257		C32H37F6N3O2	609	610

EXAMPLE 258

Trans-(*RS*)-4-(Aminomethyl)-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide

Raney nickel (10 mg) was added to a solution of *trans*-(*RS*)-4-cyano-N-{1-[3,5-bis(trifluoromethyl) phenyl]ethyl}-1-phenylcyclohexanecarboxamide (Description 29, 50 mg, 0.11 mmol) in methanolic ammonia (2M, 50 mL) and the mixture was shaken under an atmosphere of hydrogen (45 psi) for 4 hours. Further Raney nickel (10 mg) was added and the mixture was shaken under an atmosphere of hydrogen (45 psi) for 2 hours. The mixture was filtered through a glass fibre pad, washing with methanol, and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_3(Aq.) (95:5:0.5), to give the title compound.
m/z (ES$^+$) 473 (M+1).

EXAMPLE 259

Trans-(*RS*)-4-(N,N-Dimethylaminomethyl)-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide

Prepared from *trans*-(*RS*)-4-(aminomethyl)-N-{1-[3,5-bis(trifluoromethyl) phenyl]ethyl}-1-phenylcyclohexanecarboxamide (Example 258) according to the method of Example 214.
m/z (ES$^+$) 501 (M+1).

EXAMPLE 260

Trans-(*RS*)-4-[(Piperidin-1-yl)methyl]-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide

1,5-Dibromopentane (14 µl, 0.106 mmol)was added to a mixture of *trans*-(*RS*)-4-(aminomethyl)-N-{1-[3,5-bis(trifluoromethyl) phenyl]ethyl}-1-phenylcyclohexanecarboxamide (Example 258, 50 mg, 0.106 mmol), potassium carbonate (23 mg, 0.212 mmol) and sodium iodide (8 mg, 0.053 mmol) in dimethylformamide (10 mL) and the mixture was stirred at 100 °C for 5 h, then at room temperature overnight. Ether (25 mL) and water (25 mL) were added and the layers were separated. The aqueous layer was extracted with ether (25 mL) and the combined organic fractions were washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_3(Aq.) (95:5:0.5), and the residue was dissolved in methanol (0.5 mL) and poured onto an SCX cartridge (Varian Bond Elut™; 10 mL/500 mg). The cartridge was washed with methanol (2 x 5 mL), then eluted with methanolic ammonia (2M, 5 mL). The solvent was evaporated under reduced pressure to give the title compound (20 mg, 35%). m/z (ES^+) 541 (M+1).

EXAMPLE 261

Trans-(*RS*)-4-[(Morpholin-4-yl)methyl]-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide

Prepared from *trans*-(*RS*)-4-(aminomethyl)-N-{1-[3,5-bis(trifluoromethyl) phenyl]ethyl}-1-phenylcyclohexanecarboxamide (Example 258) according to the method of Example 260, substituting bis(2-bromoethyl)ether for 1,5-dibromopentane. m/z (ES^+) 543 (M+1).

EXAMPLE 262

Trans-(*RS*)-4-({N-[2-(Dimethylamino)acetyl]}aminomethyl)-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide

1-(Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (26 mg, 0.138 mmol) was added to a mixture of N,N-dimethylglycine (13 mg, 0.127 mmol), triethylamine (44 µl, 0.318 mmol) and 1-hydroxybenzotriazole (14 mg, 0.106 mmol) in dichloromethane (5 mL) and the mixture was stirred at room temperature for 10 minutes. A solution of *trans*-(*RS*)-4-(aminomethyl)-N-{1-[3,5-bis(trifluoromethyl) phenyl]ethyl}-1-phenylcyclohexanecarboxamide (Example 258, 50 mg, 0.106 mmol) in dichloromethane (6 mL) was added and the mixture was stirred at room temperature overnight. Water (25 mL) was added and the mixture was extracted with ethyl acetate (2 x 25 mL). The combined

organic fractions were washed with brine (25 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_3(Aq.) (95:5:0.5) to give the title compound (50 mg, 85%). m/z (ES^+) 558 (M+1).

EXAMPLE 263

Trans-(*RS*)-4-(1*H*-1,2,3-Triazol-1-yl)-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide

(Trimethylsilyl)acetylene (0.3 mL, 2.0 mmol) was added to a solution of *trans*-(*RS*)-4-azido-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide (Description 28, 50 mg, 0.1 mmol) in toluene and the mixture was stirred at 80 °C for 48 hours. The mixture was cooled, the solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel, eluting with isohexane/EtOAc (60:40). The residue was dissolved in tetrahydrofuran (5 mL) and acetic acid (68 µl, 1.16 mmol) and tetrabutylammonium fluoride (1M solution in tetrahydrofuran, 0.35 mL, 0.35 mmol) were added. The mixture was stirred at room temperature for 3 days and the solvent was evaporated under reduced pressure. Ethyl acetate and aqueous sodium carbonate (saturated) were added and the layers were separated. The organic layer was dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with isohexane/EtOAc (50:50), to give the title compound as a colourless foam (30 mg, 59%). m/z (ES^+) 511 (M+1), 442 (M+1-$C_2H_3N_3$).

EXAMPLE 264

Trans-N-({4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methyl)-3,5-bis(trifluoromethyl)benzenecarboxamide

3,5-Bis(trifluoromethyl)benzoyl chloride (54 µl, 0.3 mmol) was added dropwise to a solution of *trans*-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanemethanamine (Description 32, 100 mg, 0.27 mmol) in dichloromethane (5 mL) and the mixture was stirred at room temperature for 90 minutes. Water (5 mL) and saturated aqueous sodium hydrogen carbonate (2 mL) were added and the layers were separated. The aqueous layer was extracted with ethyl acetate (20 mL) and the combined organic fractions were washed with brine (10 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (0.5 mL) and poured onto an SCX cartridge (Varian Bond Elut™; 10 mL/500 mg). The cartridge was washed with methanol (2 x 5 mL), then eluted with methanolic ammonia (2M, 5 mL). The solvent was evaporated under reduced pressure to give the title compound (105 mg, 64%). m/z (ES^+) 607 (M+1).

EXAMPLE 265

Trans-N-({4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methyl)-2-(methoxy)benzenemethanamine

Sodium triacetoxyborohydride (286 mg, 1.35 mmol) was added to a solution of *trans*-4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanemethanamine (Description 32, 100 mg, 0.27 mmol) and 2-methoxybenzaldehyde (33 µl, 0.27 mmol) in dichloroethane (10 mL) and the mixture was stirred at room temperature for 24 hours. Water (10 mL) and saturated aqueous sodium hydrogen carbonate (20 mL) were added and the mixture was extracted with ethyl acetate (2 x 20 mL). The combined organic fractions were washed with brine (10 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (0.5 mL) and poured onto an SCX cartridge (Varian Bond Elut™; 10 mL/500 mg). The cartridge was washed with methanol (2 x 5 mL), then eluted with methanolic ammonia (2M, 5 mL). The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_3(Aq.) (95:5:0.5), to give the title compound (25 mg, 19%).
m/z (ES^+) 487 (M+1).

EXAMPLE 266

Cis-N-({4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methyl)-3,5-bis(trifluoromethyl)benzenemethanamine and
Trans-N-({4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methyl)-3,5-bis(trifluoromethyl)benzenemethanamine

Palladium on activated carbon (5%) was added to a solution of 4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanecarbonitrile (mixture of *cis*- and *trans*-isomers, Description 30, 180 mg, 0.5 mmol) and hydrochloric acid (conc., 5 mL) in methanol (15 mL) and the mixture was shaken under an atmosphere of hydrogen (50 psi) for 65 hours. Additional palladium on activated carbon (5%) was added and the mixture was shaken under an atmosphere of hydrogen (50 psi) for 24 hours. The mixture was filtered through a glass fibre pad, washing with methanol, and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (10 mL) and saturated aqueous sodium hydrogen carbonate (10 mL) was added. The mixture was filtered and the layers were separated. The organic layer was washed with brine (10 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (10 mL) and 3,5-bis(trifluoromethyl) benzaldehyde (42 mg, 0.17 mmol) and a mixture of sodium cyanoborohydride (11 mg, 0.17 mmol) and zinc chloride (12 mg, 0.085 mmol) in methanol

(10 mL) were added. The mixture was stirred at room temperature overnight, poured into saturated aqueous sodium hydrogen carbonate (10 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic fractions were washed with brine (10 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by preparative HPLC (ABZ+; 250 x 10.0 mm id; 34% MeCN in 0.1% TFA-H_2O; 5 ml/min; 210 nm) to give: cis-*N-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenyl cyclohexyl}methyl)-3,5-bis(trifluoromethyl)benzenemethanamine* ; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.73 (1H, s), 7.70 (2H, s), 7.38-7.33 (4H, m), 7.25-7.16 (3H, m), 6.97 (2H, t, *J* 8.7 Hz), 3.77 (2H, s), 3.08-3.00 (2H, m), 2.79 (2H, s), 2.52-2.41 (1H, m), 2.36 (2H, d, *J* 12.8 Hz), 2.30-2.17 (2H, m), 1.89-1.38 (8H, m), and 0.90-0.81 (2H, m); m/z (ES^+) 593 (M+1); trans-*N-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenyl cyclohexyl}methyl)-3,5-bis(trifluoromethyl)benzenemethanamine* ; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.71 (1H, s), 7.65 (2H, s), 7.39-7.34 (4H, m), 7.24-7.19 (1H, m), 7.15-7.11 (2H, m), 6.96-6.92 (2H, m), 3.71 (2H, m), 2.93 (2H, br d, *J* 11.5 Hz), 2.58 (2H, br d, *J* 12.4 Hz), 2.51 (2H, s), 2.40-2.35 (2H, m), 2.18-2.12 (2H, m), 1.81-1.74 (4H, m), 1.69-1.59 (2H, m), 1.48-1.40 (2H, m), and 1.35-1.26 (2H, m). m/z (ES^+) 593 (M+1).

EXAMPLE 267

Trans-N-({4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methyl)-N-methyl-3,5-bis(trifluoromethyl)benzenemethanamine

Formaldehyde (37% w/v in water, 2 mL), palladium hydroxide on carbon (20%, 10 mg) and acetic acid (24 µl, 0.42 mmol) were added to a solution of *trans*-N-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methyl)-3,5-bis(trifluoromethyl) benzenemethanamine (Example 266, 102 mg, 0.17 mmol) in methanol (10 mL) and the mixture was shaken under an atmosphere of hydrogen (50 psi) for 2.5 hours. Additional palladium hydroxide on carbon (20%, 10 mg) was added and and the mixture was shaken under an atmosphere of hydrogen (50 psi) for 1 hour. The mixture was filtered through a glass fibre pad, washing with methanol, and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (0.5 mL) and poured onto an SCX cartridge (Varian Bond Elut™; 10 mL/500 mg). The cartridge was washed with methanol (2 x 5 mL), then eluted with methanolic ammonia (2M, 5 mL). The solvent was evaporated under reduced pressure to give the title compound. m/z (ES^+) 607 (M+1).

EXAMPLE 268

Cis- and *Trans*-N-({4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methyl)-N-{[3,5-bis(trifluoromethyl)phenyl]methyl}acetamide

Prepared as a mixture of *cis*- and *trans*-isomers from N-[(4-oxo-1-phenylcyclohexyl)methyl]-N-{[3,5-bis(trifluoromethyl)phenyl]methyl}acetamide (Example 21) and 4-(4-fluorophenyl)piperidine (Description 16) according to the method of Example 55. m/z (ES^+) 635 (M+1).

EXAMPLE 269

Trans-(*RS*)-N-({4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methyl)-α-methyl-3,5-bis(trifluoromethyl)benzenemethanamine

Borane-tetrahydrofuran complex (1M in tetrahydrofuran, 0.2 mL) was added to a solution of *trans*-(*RS*)-4-[4-(4-fluorophenyl)piperidin-1-yl]-N-{1-[3,5-bis(trifluoromethyl)phenyl] ethyl}-1-phenylcyclohexanecarboxamide (Example 177, 20 mg, 0.032 mmol) in tetrahydrofuran (5 mL) and the mixture was heated under reflux for 24 hours. The mixture was cooled and methanol (10 mL) was added. The mixture was heated under reflux for 1 hour, cooled and the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water, aqueous sodium carbonate (saturated) and water, dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with CH_2Cl_2/MeOH/NH_3(Aq.) (95:5:0.5). The residue was dissolved in diethyl ether and ethereal hydrogen chloride (1M) was added. The solvent was evaporated under reduced pressure to give the title compound as a colorless solid (20 mg, 97%). m/z (ES^+) 607 (M+1).

EXAMPLE 270

Trans-(*RS*)-α-({4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl} methylamino)-3,5-bis(trifluoromethyl)benzeneethanol and

Trans-(*RS*)-α-({4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl} methylamino)-3,5-bis(trifluoromethyl)benzeneethanamine

A solution of *trans*-(*RS*)-methyl α-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}carbonylamino)-3,5-bis(trifluoromethyl)benzeneacetate (Example 157, 0.25 mmol) in methanol (1.5 mL) was poured onto an SCX cartridge (Varian Bond Elut™; 10 mL/500 mg). The cartridge was washed with methanol (4 x 1 mL), then eluted with methanolic ammonia (2M, 4 x 1 mL). The solvent was evaporated under reduced pressure and the residue was dissolved in tetrahydrofuran (4 mL) and toluene (2 mL) and lithium borohydride (10 mg, 0.46 mmol) was added. The mixture was stirred at room temperature for

30 minutes, then at 50 °C for 30 minutes. The mixture was cooled and hydrochloric acid (2M) and ethyl acetate were added. The layers were separated, the organic fraction was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was dissolved in tetrahydrofuran (2 mL) and borane-tetrahydrofuran complex (1M in tetrahydrofuran, 1 mL) was added. The mixture was stirred at 60 °C for 1 hour, then further borane-tetrahydrofuran complex (1M in tetrahydrofuran, 1 mL) was added and the mixture was stirred at 60 °C for 1 hour. The mixture was cooled and aqueous sodium carbonate (10%, 20 mL) and ethyl acetate (20 mL) were added. The layers were separated and the aqueous fraction was extracted with ethyl acetate (10 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (3 mL) and heated under reflux for 3 hours. The mixture was cooled and the solvent was evaporated under reduced pressure. The residue was dissolved in dichloromethane, filtered and the solvent was evaporated under reduced pressure. The residue was purified by preparative thin layer chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_3(Aq.) (95:5:0.5) to give:

trans-(RS)-*α-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methylamino)-3,5-bis(trifluoromethyl)benzeneethanol* (25 mg, 16%); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.75 (1H, s), 7.52 (2H, s), 7.40-7.30 (4H, m), 7.27-7.17 (1H, m), 7.20-7.10 (2H, m), 6.95 (2H, t, *J* 8.0 Hz), 3.65 (1H, dd, *J* 8.2, 4.2 Hz), 3.57 (1H, dd, *J* 10.7, 4.2 Hz), 3.31 (1H, dd, *J* 10.7, 8.2 Hz), 2.95 (2H, br d, *J* 11.0 Hz), 2.55 (2H, br d, *J* 11.0 Hz), 2.50-2.30 (2H, m), 2.46 (1H, d, *J* 11.0 Hz), 2.36 (1H, d, *J* 11.0 Hz), 2.20 (2H, br t, *J* 11.0 Hz), 2.10-1.60 (6H, m), and 1.55-1.20 (4H, m); m/z (ES$^+$) 623 (M+1); and

trans-(RS)-*α-({4-[4-(4-fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}methylamino)-3,5-bis(trifluoromethyl)benzeneethanamine*; ^{1}H NMR (360MHz, $CDCl_3$) δ 7.74 (1H, s), 7.60 (2H, s), 7.40-7.30 (4H, m), 7.27-7.17 (1H, m), 7.18-7.08 (2H, m), 6.94 (2H, t, *J* 8.0 Hz), 3.45 (1H, dd, *J* 7.6, 4.8 Hz), 2.96 (2H, br d, *J* 10 Hz), 2.77 (1H, dd, *J* 12.0, 4.8 Hz), 2.57 (1H, dd, *J* 12.0, 7.6 Hz), and 2.55-1.40 (20H, m). m/z (ES$^+$) 622 (M+1).

EXAMPLE 271

Cis- and *Trans*-(*E*)-4-(4-Fluorophenyl)-1-(4-phenyl-4-{3-[3,5-bis(trifluoromethyl)phenyl]prop-1-enyl}cyclohexyl)piperidine

Prepared as a mixture of *cis*- and *trans*-isomers from (*E*)-4-phenyl-4-{3-[3,5-bis(trifluoromethyl)phenyl]prop-1-enyl}cyclohexanone Example 22) and 4-(4-fluorophenyl)piperidine (Description 16) according to the method of Example 45. m/z (ES$^+$) 590 (M+1).

EXAMPLE 272

Cis- and *Trans*-(*E*)-4-(4-Fluorophenyl)-1-(4-phenyl-4-{3-[3,5-bis(trifluoromethyl)phenyl]propyl}cyclohexyl)piperidine

Prepared as a mixture of *cis*- and *trans*-isomers from (*E*)-4-(4-fluorophenyl)-1-(4-phenyl-4-{3-[3,5-bis(trifluoromethyl)phenyl] prop-1-enyl}cyclohexyl) piperidine (mixture of *cis*- and *trans*-isomers , Example 271) according to the method of Description 16. m/z (ES^+) 592 (M+1).

EXAMPLE 273

Cis- and *Trans*-(*RS*)-4-(4-Fluorophenyl)-1-(4-{2-hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]propyl}-4-phenylcyclohexyl)piperidine

Prepared as a mixture of *cis*- and *trans*-isomers from (*RS*)-4-{2-hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]propyl}-4-phenylcyclohexanone (Example 25) and 4-(4-fluorophenyl)piperidine (Description 16) according to the method of Example 45.

m/z (ES^+) 608 (M+1).

EXAMPLE 274

Cis- and *Trans*-(*RS*)-4-(4-Fluorophenyl)-1-(4-{2-oxo-3-[3,5-bis(trifluoromethyl)phenyl] propyl}-4-phenylcyclohexyl)piperidine

Prepared as a mixture of *cis*- and *trans*-isomers from (*RS*)-4-(4-fluorophenyl)-1-(4-{2-hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]propyl}-4-phenylcyclohexyl)piperidine (mixture of *cis*- and *trans*-isomers, Example 273) according to the method of Description 17. m/z (ES^+) 606 (M+1).

EXAMPLE 275

1-{[(1,4-Dioxa-8-phenylspiro[4.5]decan-8-yl)methoxy]methyl}-3,5-bis(trifluoromethyl) benzene

Prepared from 8-phenyl-1,4-dioxaspiro[4.5]decane-8-methanol (*J. Org.Chem.* **1974**, *39*, 2311-2313) and 1-(bromomethyl)-3,5-bis(trifluoromethyl)benzene according to the method of Example 1. ^1H NMR (360MHz, $CDCl_3$) δ 1.53-1.65 (4H, m), 1.88-1.96 (2H, m), 2.28-2.32 (2H, m), 3.42 (2H, s), 3.88-3.97 (4H, m), 4.42 (2H, s), 7.20-7.42 (5H, m), 7.55 (2H, s), and 7.72 (1H, s).

$C_{24}H_{24}F_6O_3$ requires C, 60.76, H, 5.09; found C, 61.15, H, 5.07.

EXAMPLE 276

1-({[4-Oxo-1-phenylcyclohexyl]methoxy}methyl)- 3,5-bis(trifluoromethyl)benzene

Pyridinium *p*-toluenesulfonate (100 mg, 0.4 mmol) was added to a solution of 1-{[(1,4-dioxa-8-phenylspiro[4.5]decan-8-yl)methoxy]methyl}-3,5-bis(trifluoromethyl)benzene (Example 275, 5 g, 1 mmol) in acetone -water (8:1, 9 mL) and the mixture was heated under reflux for 3 days. The mixture was cooled and the solvent was evaporated under reduced pressure. Aqueous sodium hydrogen carbonate (saturated) and ethyl acetate were added and the layers were separated. The organic fraction was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with hexane/EtOAc (70:30), to give the title compound as a colorless oil (350 mg, 83%). ^{1}H NMR (360MHz, $CDCl_3$) δ 2.06-2.10 (2H, m), 2.27-2.38 (4H, m), 2.58-2.65 (2H, m), 3.47 (2H, s), 4.44 (2H, s), 7.29-7.50 (5H, m), 7.56 (2H, s), and 7.75 (1H, s).

$C_{22}H_{20}F_6O_2$ requires C, 61.39, H, 4.68; found C, 60.92, H 4.51.

EXAMPLE 277

Cis-1-({4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanemethoxy}methyl)-3,5-bis(trifluoromethyl)benzene and

Trans-1-({4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanemethoxy}methyl)-3,5-bis(trifluoromethyl)benzene

Prepared from 1-({[4-oxo-1-phenylcyclohexyl]methoxy}methyl)- 3,5-bis(trifluoromethyl)benzene (Example 276) and 4-(4-fluorophenyl)piperidine (Description 16) according to the method of Example 45:

cis-*1-({4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanemethoxy}methyl)-3,5-bis(trifluoromethyl)benzene*; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.73 (1H, s), 7.55 (2H, s), 7.42-7.17 (7H, m), 7.00-6.95 (2H, m), 4.45 (2H, s), 3.70 (2H, s), 3.10 (2H, m), 2.47 (1H, m), 2.36-2.20 (6H, m), and 1.87-1.54 (9H, m). m/z (ES^+) 594 (M+1);

trans-*1-({4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexanemethoxy}methyl)-3,5-bis(trifluoromethyl)benzene*; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.74 (1H, s), 7.57 (2H, s), 7.39 (4H, m), 7.24 (1H, m), 7.15 (2H, dd, *J* 8.6, 5.4 Hz), 6.95 (2H, t, *J* 8.6 Hz), 4.42 (2H, s), 3.33 (2H, s), 3.04 (2H, m), 2.75-1.62 (14H, m), and 1.39 (2H, m). m/z (ES^+) 594 (M+1).

EXAMPLE 278

(*RS*)-4-Methylene-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl} cyclohexanecarboxamide

Methyltriphenylphosphonium bromide (1.71 g, 4.8 mmol) was dried azeotropically by evaporating toluene (3 x 20 mL) under reduced pressure, suspended in tetrahydrofuran

(20 mL) and cooled in ice. Butyllithium (1.6M in hexanes, 3.0 mL, 4.8 mmol) was added and the mixture was stirred at room temperature for 3 hours. The mixture was cooled in ice and (*RS*)-4-oxo-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl} cyclohexanecarboxamide (Example 18, 0.91 g, 2.0 mmol) in tetrahydrofuran (5 mL) was added. The mixture was stirred at room temperature for 1 hour, then heated under reflux for 3 hours. The mixture was cooled, poured into water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic fractions were washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with CH_2Cl_2, to give the title compound as a colorless solid (0.67 g, 73%); ^{1}H NMR (400MHz, CD_3OD) δ 7.76 (1H, s), 7.69 (2H, s), 7.34-7.20 (5H, m), 5.14 (1H, q, *J* 7.1 Hz), 4.64 (2H, s), 2.53 (2H, m), 2.27 (4H, m), 1.99 (1H, m), 1.77 (1H, m), and 1.42 (3H, d, J 7.1 Hz).

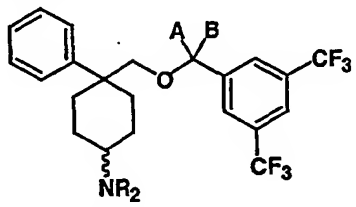
EXAMPLE 279

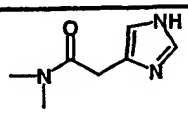
Cis-(*RS*)-4-(Hydroxymethyl)-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide and
Trans-(*RS*)-4-(Hydroxymethyl)-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide

9-Borabicyclo[3.3.1]nonane (0.5M in tetrahydrofuran, 1.0 mL, 0.5 mmol) was added to a solution of (*RS*)-4-methylene-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl} cyclohexanecarboxamide (Example 278, 182 mg, 0.4 mmol) in tetrahydrofuran (2 mL) and the mixture was stirred at room temperature for 2 hours. Ethanol (0.5 mL), aqueous sodium hydroxide (4M, 0.2 mL) and aqueous hydrogen peroxide (35%, 0.2 mL) were added and the mixture was stirred at 50 °C for 1 hour. The mixture was cooled, poured into aqueous sodium hydrogen carbonate (saturated, 20 mL) and water (10 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic fractions were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by MPLC chromatography on silica gel, eluting with isohexane/EtOAc (70:30 increasing to 50:50), to give:
cis-(RS)-*4-(hydroxymethyl)-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide* (113 mg, 60%), ^{1}H NMR (400MHz, CD_3OD) δ 7.76 (1H, s), 7.71 (2H, s), 7.31 (2H, d, *J* 7.5 Hz), 7.25 (2H, t, *J* 7.5 Hz), 7.20 (1H, t, *J* 7.5 Hz), 5.14 (1H, q, *J* 7.1 Hz), 3.32 (2H, m), 2.67 (2H, m), 1.89-1.48 (5H, m), 1.43 (3H, d, J 7.1 Hz), and 1.24-1.09 (2H, m); and
trans-(RS)-*4-(hydroxymethyl)-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}-1-phenylcyclohexanecarboxamide* (34 mg, 18%), ^{1}H NMR (400MHz, CD_3OD) δ 7.73 (1H, s), 7.61 (2H, s), 7.44 (2H, d, *J* 7.5 Hz), 7.34 (2H, t, *J* 7.5 Hz), 7.23 (1H, t, *J* 7.5 Hz), 5.03 (1H, q,

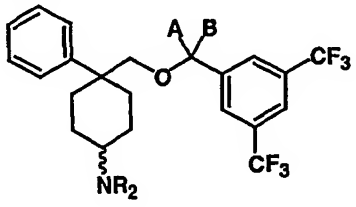
J 7.0 Hz), 3.29 (2H, d, *J* 6.6 Hz), 2.68 (1H, m), 2.54 (1H, m), 1.90 (2H, m), 1.72 (2H, m), 1.56 (1H, m), 1.39 (3H, d, *J* 7.0 Hz), 1.20 (1H, m), and 1.07 (1H, m).

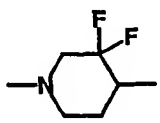
The following compound was prepared from *trans*-(*RS*)-β-[(4-methylamino-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol (Example 90) and 1H-imidazole-4-acetic acid according to the method of Example 91.

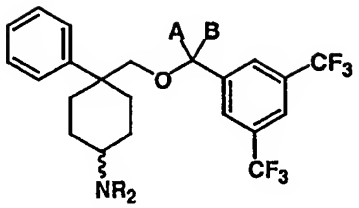


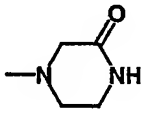
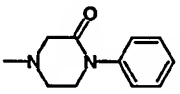
Ex.	A	B	-NR_2	Stereochemistry	Formula	M.W.	m/z (ES⁺) (M+1).
280	CH_2O H	H		*Trans*-(*RS*)-	$C_{29}H_{31}F_6N_3O_3$	583	584

The following compounds were prepared according to the method of Example 45, substituting a suitable ketone for (*RS*)-β-[(4-oxo-1-phenylcyclohexyl)methoxy]-3,5-bis(trifluoromethyl)benzeneethanol, and a suitable amine for benzylamine, followed by separation of diastereoisomers by chromatography on silica gel.

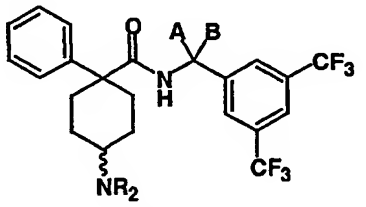


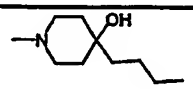
Ex.	A	B	-NR_2	Stereochemistry	Formula	M.W.	m/z (ES⁺) (M+1).
281	H	H		*Cis*-(*RS*)-	$C_{30}H_{35}F_6NO_2$	555	556
282	H	H		*Trans*-(*RS*)-	$C_{30}H_{35}F_6NO_2$	555	556
283	Me	H		*Trans*-(*RS*)-	$C_{29}H_{33}F_8NO$	563	564

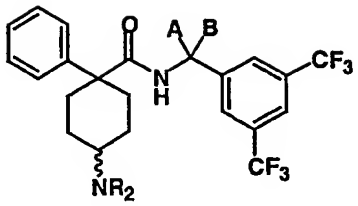


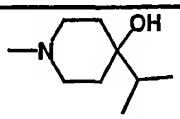
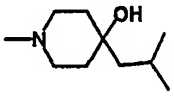
Ex.	A	B	-NR_2	Stereochemistry	Formula	M.W.	m/z (ES^+) (M+1).
284	Me	H		*Cis*-(*RS*)-	$C_{31}H_{37}F_6NO_2$	569	570
285	Me	H		*Trans*-(*RS*)-	$C_{31}H_{37}F_6NO_2$	569	570
286	Me	H		*Trans*-(*RS*)-	$C_{27}H_{30}F_6N_2O_2$	528	529
287	Me	H		*Trans*-(*RS*)-	$C_{33}H_{34}F_6N_2O_2$	604	605
288	CH_2O H	H		*Cis*-(*RS*)-	$C_{31}H_{37}F_6NO_3$	585	586
289	CH_2O H	H		*Trans*-(*RS*)-	$C_{31}H_{37}F_6NO_3$	585	586

The following compounds were prepared from *trans*-(*RS*)-4-(4-oxopiperidin-1-yl)-1-phenyl-N-{1-[3,5-bis(trifluoromethyl)phenyl]ethyl}cyclohexanecarboxamide (Example 184) according to the method of Example 187, substituting a suitable Grignard reagent for phenylmagnesium bromide.



Ex.	A	B	-NR_2	Stereochemistry	Formula	M.W.	m/z (ES^+) (M+1).
290	Me	H		*Trans*-(*RS*)-	$C_{32}H_{40}F_6N_2O_2$	598	599



Ex.	A	B	-NR_2	Stereochemistry	Formula	M.W.	m/z (ES^+) (M+1).
291	Me	H		*Trans*-(*RS*)-	$C_{31}H_{38}F_6N_2O_2$	584	585
292	Me	H		*Trans*-(*RS*)-	$C_{32}H_{40}F_6N_2O_2$	598	599
293	Me	H		*Trans*-(*RS*)-	$C_{30}H_{36}F_6N_2O_2$	570	571

EXAMPLE 294

Cis-(*RS*)- and *Trans*-(*RS*)-1-(4-{2-hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]propyl}-4-phenylcyclohexyl)piperidine

Prepared as a 1:1 mixture of diastereoisomers from (*RS*)-4-{2-hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]propyl}-4-phenylcyclohexanone (Example 25) and piperidine according to the method of Example 45. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.68 (1H, s), 7.50 and 7.48 (Total 2H, each s), 7.4-7.25 (4H, m), 7.25-7.15 (1H, m), 3.80-3.70 and 3.70-3.60 (Total 1H, each m), and 2.75-1.20 (23H, m). m/z (ES^+) 514 (M+1).

EXAMPLE 295

(*RS*)-1-(8-Phenyl-1,4-dioxaspiro[4.5]decan-8-yl)-3-[3,5-bis(trifluoromethyl)phenyl]propan-1-ol

Potassium carbonate (1.75 g, 12.7 mmol) was added to a solution of (*RS*)-1-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)-3-[3,5-bis(trifluoromethyl)phenyl]propan-1-yl ethanoate (Example 23, 410 mg, 0.773 mmol) in methanol (15 mL) and water (2 mL) and the mixture was stirred at room temperature for 48 hours, then at 50 °C for 24 hours. The mixture was cooled and the methanol was evaporated under reduced pressure. Water (50 mL) was added and the mixture was extracted with ethyl acetate (2 x 50 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure to give the title compound (334 mg, 88%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.68 (1H, s), 7.53 (2H, s), 7.4-7.3 (4H, m),

7.3-7.2 (1H, m), 3.95-3.8 (4H, m), 3.36 (1H, br d, *J* 9 Hz), 2.91 (1H, ddd, *J* 14, 10, 5 Hz), 2.64 (1H, ddd, *J* 16, 9, 7.5 Hz), 2.5-2.4 (1H, m), 2.3-2.2 (1H, m), 1.9-1.7 (3H, m), and 1.65-1.20 (6H, m).

EXAMPLE 296

(RS)-4-{1-Hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]propyl}-4-phenylcyclohexanone

Prepared from (*RS*)-1-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)-3-[3,5-bis(trifluoromethyl)phenyl]propan-1-ol (Example 295) according to the method of Example 10. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.69 (1H, s), 7.51 (2H, s), 7.5-7.4 (4H, m), 7.35-7.25 (1H, m), 3.44 (1H, br d, *J* 11 Hz), 2.93 (1H, ddd, *J* 14, 10, 5 Hz), 2.8-2.7 (1H, m), 2.7-2.6 (1H, m), 2.6-2.5 (1H, m), 2.4-2.2 (4H, m), 2.05-1.9 (2H, m), 1.85-1.75 (1H, m), and 1.45-1.3 (2H, m).

EXAMPLE 297

Trans-(*RS*)-1-(4-{1-hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]propyl}-4-phenylcyclohexyl)piperidine

Prepared from (*RS*)-4-{1-hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]propyl}-4-phenylcyclohexanone (Example 296) and piperidine according to the method of Example 45, followed by separation of diastereoisomers by chromatography on silica gel. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.67 (1H, s), 7.51 (2H, s), 7.4-7.3 (4H, m), 7.3-7.2 (1H, m), 3.30 (1H, br d, *J* 11 Hz), 2.90 (1H, ddd, *J* 14, 10, 5 Hz), 2.7-2.55 (2H, m), 2.45-2.3 (8H, m), 1.85-1.75 (3H, m), and 1.7-1.2 (10H, m). m/z (ES^+) 514 (M+1).

EXAMPLE 298

Cis-(*RS*)-4-(4-Fluorophenyl)-1-(4-{1-hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]propyl}-4-phenylcyclohexyl)piperidine; and

Trans-(*RS*)-4-(4-Fluorophenyl)-1-(4-{1-hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]propyl}-4-phenylcyclohexyl)piperidine

Prepared from (*RS*)-4-{1-hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]propyl}-4-phenylcyclohexanone (Example 296) and 4-(4-fluorophenyl)piperidine (Description 16) according to the method of Example 45, followed by separation by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH/NH_3(Aq.) (97.5:2.5:0.25 increasing to 95:5:0.5), to give cis-(RS)-*4-(4-fluorophenyl)-1-(4-{1-hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]propyl}-4-phenylcyclohexyl)piperidine*; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.68 (1H, s), 7.58 (2H, s), 7.4-7.3 (4H, m), 7.3-7.25 (1H, m), 7.25-7.15 (2H, m), 6.99 (2H, t, *J* 9 Hz), 3.85 (1H, br d, *J* 10 Hz), 3.25-3.05 (2H, m), 2.95-2.85 (1H, m), 2.78-2.62

(2H, m), 2.50 (1H, quin, *J* 7 Hz), 2.45-2.15 (4H, m), 1.9-1.4 (12H, m), and 1.2-1.08 (1H, m); m/z (ES^+) 608 (M+1); and. trans-(RS)-*4-(4-fluorophenyl)-1-{4-[1-hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]propyl}-4-phenylcyclohexyl)piperidine*; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.67 (1H, s), 7.52 (2H, s), 7.4-7.3 (4H, m), 7.3-7.2 (1H, m), 7.13 (2H, dd, *J* 8.7, 5.5 Hz), 6.94 (2H, t, *J* 8.7 Hz), 3.31 (1H, br d, *J* 10.5 Hz), 3.0-2.85 (3H, m), 2.69-2.58 (2H, m), 2.55-2.35 (3H, m), 2.3-2.1 (2H, m), 1.9-1.5 (9H, m), and 1.4-1.2 (4H, m); m/z (ES^+) 608 (M+1).

EXAMPLE 299

Trans-4-(4-Fluorophenyl)-1-(4-{1-oxo-3-[3,5-bis(trifluoromethyl)phenyl]propyl}-4-phenylcyclohexyl)piperidine

1,1,1-Tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one (28 mg, 0.066 mmol) was added to a solution of *trans*-(*RS*)-4-(4-fluorophenyl)-1-(4-{1-hydroxy-3-[3,5-bis(trifluoromethyl)phenyl]propyl}-4-phenylcyclohexyl)piperidine (Example 298, 14 mg, 0.023 mmol) in dichloromethane (2 mL) and the mixture was stirred at room temperature for 2 hours. Saturated aqueous sodium bisufite (1 mL) and aqueous sodium hydrogen carbonate (5%, 15 mL) were added and the mixture was stirred at room temperature for 20 minutes. The layers were separated and the aqueous layer was extracted with dichloromethane (2 mL). The combined organic fractions were poured onto an SCX cartridge (Varian Bond Elut™; 10 mL/500 mg). The cartridge was washed with methanol (4 x 2 mL), then eluted with methanolic ammonia (2M, 2 x 2 mL). The solvent was evaporated under reduced pressure to give the title compound (13.1 mg, 94%). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.61 (1H, s), 7.35 (2H, s), 7.28-7.08 (7H, m), 6.95 (2H, t, *J* 9 Hz), 2.95 (2H, br d, *J* 11 Hz), 2.80 (2H, t, *J* 7 Hz), 2.6-2.5 (2H, m), 2.54 (2H, t, *J* 7 Hz), 2.45-2.30 (2H, m), 2.15 (2H, t, *J* 11 Hz), 1.9-1.5 (8H, m), and 1.5-1.35 (2H, m). m/z (ES^+) 606 (M+1).

EXAMPLE 300

(*RS*)-1-(4-Oxo-1-phenylcyclohexyl)-3-[3,5-bis(trifluoromethyl)phenyl]propan-2-yl Ethanoate

Prepared from (*RS*)-1-(8-phenyl-1,4-dioxaspiro[4.5]decan-8-yl)-3-[3,5-bis(trifluoromethyl)phenyl]propan-2-yl ethanoate (Example 23) according to the method of Example 10. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.69 (1H, s), 7.38 (2H, s), 7.36-7.20 (5H, m), 4.95-4.85 (1H, m), 2.73 (1H, dd, *J* 14, 7 Hz), 2.62-2.47 (2H, m), 2.46 (1H, dd, *J* 14, 6 Hz), 2.35-2.20 (4H, m), 2.02 (1H, dd, *J* 14, 7 Hz), 1.95-1.80 (2H, m), 1.77 (1H, dd, *J* 14, 3 Hz), and 1.75 (3H, m).

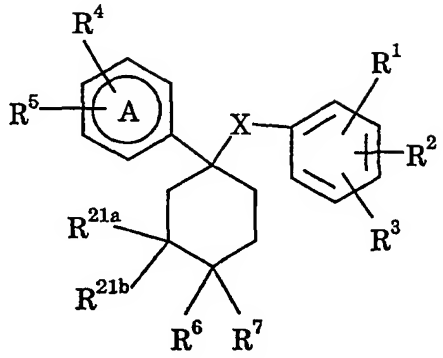
EXAMPLE 301

Trans-(*RS*)-1-{4-[4-(4-Fluorophenyl)piperidin-1-yl]-1-phenylcyclohexyl}-3-[3,5-bis(trifluoromethyl)phenyl]propan-2-yl Ethanoate

Prepared from (*RS*)-1-(4-oxo-1-phenylcyclohexyl)-3-[3,5-bis(trifluoromethyl)phenyl]propan-2-yl ethanoate (Example 300) and 4-(4-fluorophenyl)piperidine (Description 16) according to the method of Example 45, followed by separation of diastereoisomers by flash column chromatography on silica gel, eluting with CH_2Cl_2/MeOH (95:5). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.68 (1H, s), 7.36 (2H, s), 7.32-7.10 (7H, m), 6.92 (2H, t, *J* 9 Hz), 4.92-4.82 (1H, m), 3.01 (2H, br d, *J* 9 Hz), 2.66 (1H, dd, *J* 14, 7 Hz), 2.6-2.2 (6H, m), 2.40 (1H, dd, *J* 14, 6 Hz), 2.10-1.70 (7H, m), 1.74 (3H, s), 1.64 (1H, dd, *J* 14, 3 Hz), and 1.55-1.22 (4H, m). m/z (ES^+) 650 (M+1).

CLAIMS:

1. A compound of the formula (I):

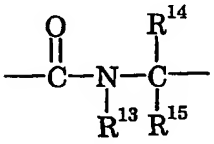


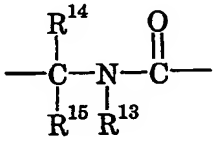
(I)

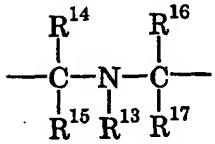
wherein

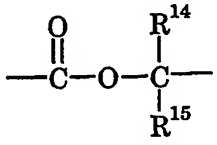
ring A is a phenyl or pyridyl ring;

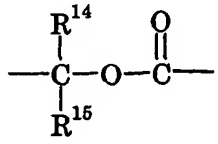
X represents a linker selected from the group consisting of:

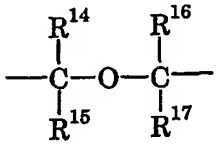
(a)  ,

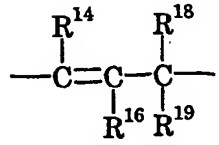
(b)  ,

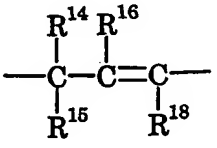
(c)  ,

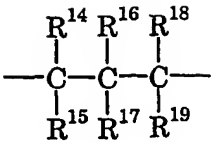
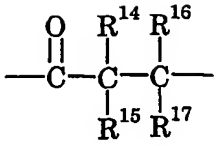
(d)  ,

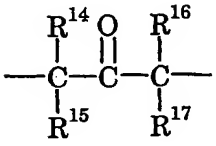
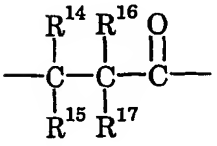
(e)  ,

(f)  ,

(g)  ,

(h)  ,

(i)  , (j)  ,

(k)  , and (l)  ;

R¹ represents hydroxy, C_{1-6}alkyl, fluoroC_{1-6}alkyl, C_{2-6}alkenyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkoxy, C_{1-6}alkoxyC_{1-4}alkyl, C_{1-6}alkoxyC_{1-4}alkoxy, fluoroC_{1-6}alkoxyC_{1-4}alkyl, C_{2-6}alkenyloxy, C_{3-7}cycloalkoxy, C_{3-7}cycloalkylC_{1-4}alkoxy, phenoxy, cyano, halogen, NR^aR^b, SR^a, SOR^a, SO_2R^a, OSO_2R^a, NR^aCOR^c, COR^a, CO_2R^a or $CONR^aR^b$ where R^a and R^b each independently represent hydrogen, C_{1-4}alkyl, C_{3-5}cycloalkyl, fluoroC_{1-4}alkyl or $CH_2CO_2C_{1-4}$alkyl, and R^c represents C_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkyl or phenyl;

R² represents hydrogen, halogen, C_{1-6}alkyl or C_{1-6}alkoxy;

or when R² is adjacent to R¹, they may be joined together such that there is formed a 5- or 6-membered saturated or unsaturated ring containing one or two atoms selected from nitrogen, oxygen and sulphur, which ring is optionally substituted by a group selected from C_{1-4}alkyl, CF_3, =O or =S;

R³ represents hydrogen, halogen, C_{1-6}alkyl, fluoroC_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkoxy, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, cyano, SR^a, SOR^a, SO_2R^a, NR^aR^b, NR^aCOR^{14}, COR^a, CO_2R^a, $CONR^aR^b$ or C_{1-4}alkyl substituted by cyano, CO_2R^a or $CONR^aR^b$ where R^a and R^b are as previously defined;

or R³ represents a 5- or 6-membered aromatic heterocyclic group containing 1, 2, 3 or 4 heteroatoms, selected from nitrogen, oxygen and sulphur, which group is optionally substituted by one or two groups selected from C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, trifluoromethyl, OCF_3, NO_2, CN, SR^a, SOR^a, SO_2R^a, COR^a, CO_2R^a, phenyl, $-(CH_2)_rNR^aR^b$, $-(CH_2)_rNR^aCOR^b$, $-(CH_2)_rCONR^aR^b$, or $CH_2C(O)R^a$, where R^a and R^b are as previously defined and r is zero, 1 or 2;

R^4 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy, hydroxy, NO_2, CN, SR^a, SOR^a, SO_2R^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl substituted by C_{1-4}alkoxy, wherein R^a and R^b are as previously defined;

R^5 is hydrogen, halogen, C_{1-6}alkyl, fluoroC_{1-6}alkyl or C_{1-6}alkoxy substituted by C_{1-4}alkoxy;

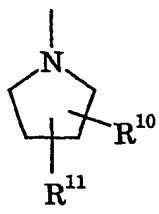
R^6 represents hydrogen, hydroxy or a C_{1-4}alkyl group optionally substituted by a hydroxy group;

R^7 represents hydrogen, hydroxy, $-(CH_2)_nNR^8R^9$, $-(CH_2)_nCO_2R^a$, carbocyclyl, C-linked heterocyclyl or heteroaryl;

or R^6 and R^7 together represent =O, $=CHCO_2R^a$ or $-O(CH_2)_mO-$;

R^8 and R^9 each independently represent hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, hydroxyC_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl, $(CH_2)_q$heterocyclyl, CHO, $C(O)C_{1-6}$alkyl, $C(O)(CH_2)_qC_{3-7}$cycloalkyl, $C(O)(CH_2)_q$aryl, $C(O)(CH_2)_q$heterocyclyl, $C(O)(CH_2)_pNR^aR^b$, $(CH_2)_qCO_2C_{1-6}$alkyl, $CO_2(CH_2)_qC_{3-7}$cycloalkyl, $CO_2(CH_2)_q$aryl, $CO_2(CH_2)_q$heterocyclyl, $CO_2(CH_2)_pNR^aR^b$, $(CH_2)_pNR^aCOR^b$, $(CH_2)_pNR^aCO_2R^b$, $(CH_2)_qCONR^a$aryl or $(CH_2)_qCONR^a$heterocyclyl where R^a and R^b are as previously defined;

or R^8 and R^9, together with the nitrogen atom to which they are attached, represent a heteroaliphatic ring selected from the group consisting of: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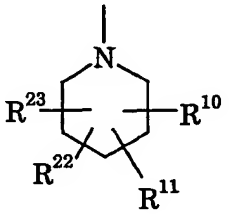
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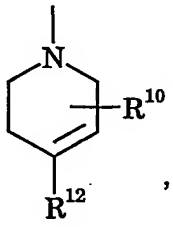
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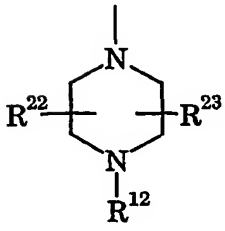
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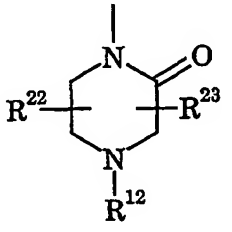
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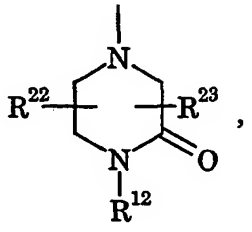
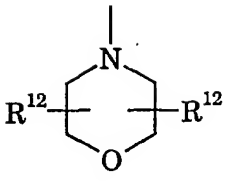
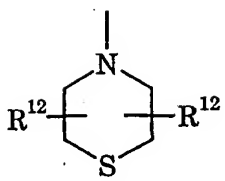

,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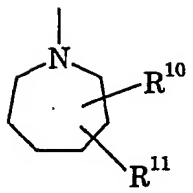
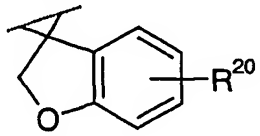

;

R^{10} and R^{11} each independently represent hydrogen, halogen, hydroxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, hydroxyC_{1-6}alkyl, fluoroC_{1-6}alkyl, C_{1-6}alkoxy, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl, (C_{2-6}alkenyl)aryl, (C_{2-6}alkynyl)aryl, $(CH_2)_q$heterocyclyl, $(CH_2)_qNR^aR^b$, $O(CH_2)_qC_{3-7}$cycloalkyl, $O(CH_2)_q$aryl, $O(CH_2)_q$heterocyclyl, $O(CH_2)_pNR^aR^b$, $OC(O)C_{1-6}$alkyl, $C(O)C_{1-6}$alkyl, $C(O)(CH_2)_q$aryl, $C(O)(CH_2)_q$heterocyclyl, $C(O)(CH_2)_qNR^aR^b$, CO_2H, CO_2C_{1-6}alkyl, $CO_2(CH_2)_qC_{3-7}$cycloalkyl, $CO_2(CH_2)_q$aryl, $CO_2(CH_2)_q$heterocyclyl or $CO_2(CH_2)_pNR^aR^b$, where R^a and R^b are as previously defined;

or, when they are attached to the same carbon atom, R^{10} and R^{11} may together represent =O, $=CHCO_2R^a$, $-O(CH_2)_mO-$, $-CH_2O(CH_2)_s-$, $-CH_2OCH_2C(O)-$, $-CH_2OCH_2CH(OH)-$, $-CH_2OCH_2C(CH_3)_2-$, $-CH_2OC(CH_3)_2CH_2-$, $-C(CH_3)_2OCH_2CH_2-$, $-CH_2C(O)OCH_2-$, $-OC(O)CH_2CH_2-$, $-C(O)OCH_2CH_2-$, $-C(O)OC(CH_3)_2CH_2-$, $-C(O)OCH_2C(CH_3)_2-$, $-OCH_2(CH_2)_s-$, $-OC(CH_3)_2CH_2CH_2-$, $-OCH_2C(CH_3)_2CH_2-$, $-OCH_2CH_2C(CH_3)_2-$, $-OCH_2CH=CHCH_2-$, $-OCH_2CH(OH)CH_2CH_2-$, $-OCH_2CH_2CH(OH)CH_2-$, $-OCH_2C(O)CH_2CH_2-$, $-OCH_2CH_2C(O)CH_2-$, or a group of the formula


;

or, where they are attached to adjacent carbon atoms, R^{10} and R^{11} may together represent $-OCH_2CH_2-$ or $-OCH_2CH(OH)-$, or R^{10} and R^{11} may together form a fused benzene ring;

or, R^{10} and R^{11} together form a C_{1-2}alkylene bridge across the pyrrolidine, piperidine or hexamethyleneimine ring to which they are attached;

R^{12} represents hydrogen, C_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl, $(CH_2)_q$heterocyclyl, CHO, $C(O)C_{1-6}$alkyl, $C(O)(CH_2)_qC_{3-7}$cycloalkyl, $C(O)(CH_2)_q$aryl, $C(O)(CH_2)_q$heterocyclyl, CO_2C_{1-6}alkyl, $CO_2(CH_2)_qC_{3-7}$cycloalkyl, $CO_2(CH_2)_q$aryl,

$CO_2(CH_2)_q$heterocyclyl or $CO_2(CH_2)_pNR^aR^b$, where R^a and R^b are as previously defined;

or, where they are attached to adjacent carbon atoms, R^{12} and R^{18} may together form a fused imidazolyl or triazolyl ring;

R^{13} represents hydrogen, C_{1-6}alkyl or $C(O)C_{1-6}$alkyl;

R^{14}, R^{15}, R^{16}, R^{17}, R^{18} and R^{19} each independently represent hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkenyl, hydroxyC_{1-6}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, $(CH_2)_pNR^aR^b$, CHO, $C(O)C_{1-6}$alkyl or CO_2C_{1-6}alkyl;

or, R^{14} and R^{15} together represent $-CH_2CH_2-$;

or, R^{16} and R^{17} together represent $-CH_2CH_2-$;

or, R^{18} and R^{19} together represent $-CH_2CH_2-$;

R^{20} represents hydrogen, halogen, hydroxy, C_{1-4}alkyl, hydroxyC_{1-4}alkyl or fluoroC_{1-4}alkyl;

R^{21a} represents hydrogen, halogen or hydroxy and R^{21b} represents hydrogen;

or R^{21a} and R^{21b} both represent fluorine or together represent oxo (=O);

R^{22} and R^{23} each independently represent hydrogen, halogen, hydroxy, C_{1-6}alkyl or oxo (=O);

n is zero, 1 or 2;

m is 1 or 2;

p is 1, 2, 3 or 4;

q is zero, 1, 2, 3 or 4; and

s is 1, 2 or 3;

and pharmaceutically acceptable salts and N-oxides thereof.

2. A compound as claimed in Claim 1 wherein R^1 is hydroxy, C_{1-6}alkyl, fluoroC_{1-6}alkyl, C_{2-6}alkenyl, C_{1-6}alkoxy, fluoroC_{1-6}alkoxy, C_{2-6}alkenyloxy, C_{3-7}cycloalkoxy, C_{3-7}cycloalkylC_{1-4}alkoxy, cyano, NR^aR^b, SR^a, OSO_2R^a, or R^1 together with the group R^2 form a 5-membered saturated ring containing one oxygen atom.

3. A compound as claimed in Claim 1 or Claim 2 wherein R^2 is a hydrogen, fluorine or chl rine atom, especially a hydrogen atom.

4. A compound as claimed in any one of Claims 1 to 3 wherein R^3 is hydrogen, halogen, fluoroC_{1-6}alkyl, fluoroC_{1-6}alkoxy, cyano, NR^aR^b, NR^aCOR^d (where R^d is methyl, methoxy, trifluoromethyl or phenyl), or a 5-membered aromatic heterocyclic group as defined in Claim 1.

5. A compound as claimed in any one of Claims 1 to 4 wherein R^4 is hydrogen.

6. A compound as claimed in any one of Claims 1 to 5 wherein R^5 is hydrogen, fluorine, chlorine or CF_3.

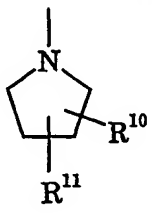
7. A compound as claimed in any one of Claims 1 to 6 wherein R^6 is hydrogen.

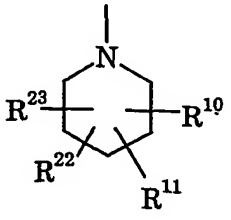
8. A compound as claimed in any one of Claims 1 to 7 wherein R^7 is hydroxy, $-(CH_2)_nNR^8R^9$, a C-linked heterocyclyl group or R^6 and R^7 together represent =O, $-O(CH_2)_mO-$ or $-CH_2OCH_2C(O)-$.

9. A compound as claimed in Claim 8 wherein R^8 represents hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl, hydroxyC_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl, $(CH_2)_q$heterocyclyl, $C(O)C_{1-6}$alkyl, $C(O)(CH_2)_q$aryl, $C(O)(CH_2)_q$heterocyclyl, $C(O)(CH_2)_pNR^aR^b$, $(CH_2)_qCO_2C_{1-6}$alkyl, $(CH_2)_pNR^aCO_2R^b$ or $(CH_2)_qCONR^a$aryl;

and R^9 represents hydrogen, C_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl or CO_2C_{1-6}alkyl;

or R^8 and R^9 together with the nitrogen atom to which they are attached represent a heteroaliphatic ring selected from the group consisting of



,


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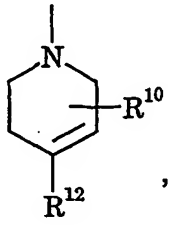

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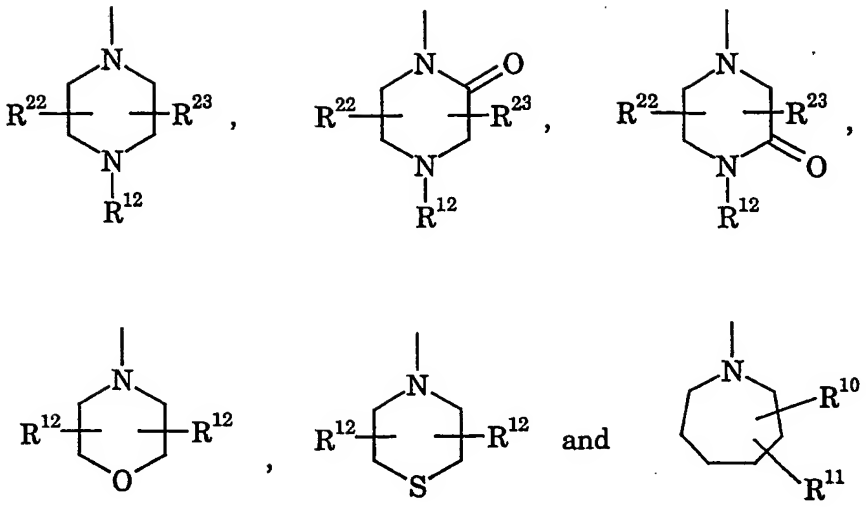
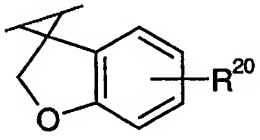


10. A compound as claimed in Claim 9 wherein R^{10} represents hydrogen, hydroxy, C_{1-6}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, hydroxyC_{1-6}alkyl, fluoroC_{1-6}alkyl, (C_{2-6}alkynyl)aryl, $(CH_2)_q$aryl, $(CH_2)_q$heterocyclyl, $(CH_2)_qNR^aR^b$, $OC(O)C_{1-6}$alkyl, $C(O)(CH_2)_qNR^aR^b$, CO_2H or CO_2C_{1-6}alkyl;

and R^{11} represents hydrogen, halogen, hydroxy, C_{1-6}alkyl or $(CH_2)_q NR^aR^b$;

or when they are attached to the same carbon atom, R^{10} and R^{11} may together represent =O, $-O(CH_2)_mO-$, $-CH_2O(CH_2)_s-$, $-CH_2OCH_2C(O)-$, $-CH_2OCH_2CH(OH)-$, $-CH_2OCH_2C(CH_3)_2-$, $-CH_2OC(CH_3)_2CH_2-$, $-C(CH_3)_2OCH_2CH_2-$, $-CH_2C(O)OCH_2-$, $-OC(O)CH_2CH_2-$, $-C(O)OCH_2CH_2-$, $-C(O)OC(CH_3)_2CH_2-$, $-C(O)OCH_2C(CH_3)_2-$, $-OCH_2(CH_2)_s-$, $-OC(CH_3)_2CH_2CH_2-$, $-OCH_2CH=CHCH_2-$, $-OCH_2CH(OH)CH_2CH_2-$, $-OCH_2CH_2CH(OH)CH_2-$, $-OCH_2C(O)CH_2CH_2-$, or a group of the formula



;

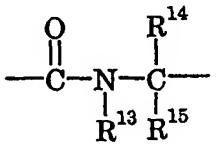
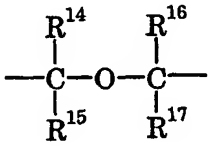
or, when they are attached to adjacent carbon atoms, R^{10} and R^{11} may together represent $-OCH_2CH_2-$ or $-OCH_2CH(OH)-$, or R^{10} and R^{11} may together form a fused benzene ring;

or R^{10} and R^{11} together form a C_{1-2}alkylene bridge across the pyrrolidine or piperidine ring to which they are attached.

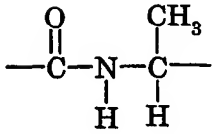
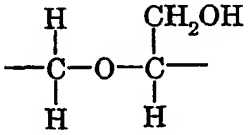
11. A compound as claimed in Claim 9 wherein R^{12} represents hydrogen, C_{1-6}alkyl, $(CH_2)_qC_{3-7}$cycloalkyl, $(CH_2)_q$aryl, $(CH_2)_q$heterocyclyl, CHO, $C(O)C_{1-6}$alkyl, $C(O)C_{3-7}$cycloalkyl, $C(O)(CH_2)_q$aryl or CO_2C_{1-6}alkyl.

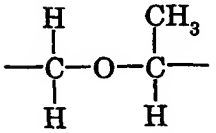
12. A compound as claimed in any one of Claims 1 to 11 wherein the ring A is a phenyl ring.

13. A compound as claimed in any one of Claims 1 to 12 wherein X is a linker selected from:

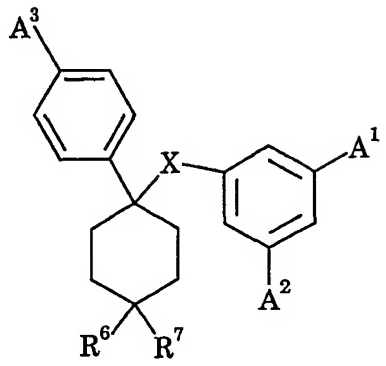
(a)  , and (b)  .

14. A compound as claimed in Claim 13 wherein X is a linker selected from:

(a)  , (b)  , and

(c)  .

15. A compound of the formula (Ia):



(Ia)

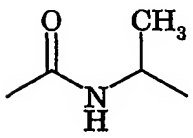
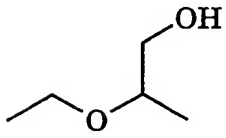
wherein

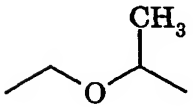
A^1 is fluorine or CF_3;

A^2 is fluorine or CF_3;

A^3 is fluorine or hydrogen;

X is a linker selected from:

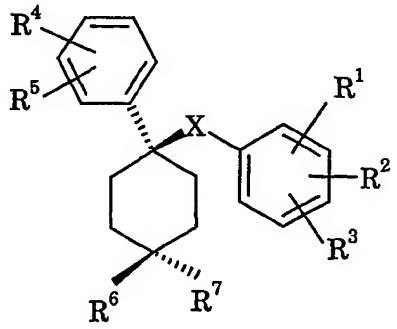
(a)  , (b)  , and

(c)  ; and

R^6 and R^7 are as defined in Claim 1;

or a pharmaceutically acceptable salt thereof.

16. A compound as claimed in any one of Claims 1 to 14 wherein the stereochemistry of the 1- and 4-positions is as shown in formula (Ib):



(Ib)

17. A compound as claimed in any preceding claim for use in therapy.

18. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1 to 16, together with at least one pharmaceutically acceptable carrier or excipient.

19. A method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound according to Claim 1.

20. A method according to Claim 19 for the treatment or prevention of pain or inflammation, migraine, emesis, postherpetic neuralgia, depression or anxiety.

21. The use of a compound as claimed in any one of Claims 1 to 16 for the manufacture of a medicament for the treatment or prevention of a physiological disorder associated with an excess of tachykinins.

22. The use of a compound as claimed in any one of Claims 1 to 16 for the manufacture of a medicament for th treatment or prevention of pain or inflammation, migraine, emesis, postherpetic neuralgia, depression or anxiety.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D295/16 A61K31/495 A61K31/44 A61K31/4427 A61K31/16
A61P25/24 A61P25/04 A61P1/08 C07D295/12 C07D211/58
C07D471/10 C07D401/06 C07C217/52 C07C237/06 C07D295/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 25770 A (MERCK & CO., INC., USA) 11 May 2000 (2000-05-11) claims; examples	1-22
X	US 4 611 004 A (ACKERMANN, PETER ET AL) 9 September 1986 (1986-09-09) claims 1,10; examples 8,12,22	1-14
X	JP 59 116243 A (MITSUI TOATSU CHEMICALS, INC., JAPAN) 5 July 1984 (1984-07-05) examples 1,38 see formula (I) page 345	1-13

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 July 2001	13/08/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schmid, J-C

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 84, no. 23, 7 June 1976 (1976-06-07) Columbus, Ohio, US; abstract no. 164575, MARKARYAN, E. A. ET AL: "Isoquinoline derivatives. XI. Synthesis and pharmacological activity of 1-arylalkyl-4-spirocyclohexane-6,7-dimetho xy-1,2,3,4- tetrahydroisoquinolines and some of their derivatives" XP002172979 see formula II abstract & ARM. KHIM. ZH. (1975), 28(10), 829-35, ---	1-12
A	US 5 849 795 A (ARCAMONE FEDERICO ET AL) 15 December 1998 (1998-12-15) the whole document ---	1-22
A	STEVENTON ET AL: "4,4-disubstituted Piperidine High-Affinity NK1 Antagonists: Structure-Activity Relationships and in Vivo Activity" JOURNAL OF MEDICINAL CHEMISTRY,AMERICAN CHEMICAL SOCIETY. WASHINGTON,US, vol. 41, no. 23, 1998, pages 4623-4635, XP002173109 ISSN: 0022-2623 the whole document ---	1-22
P,X	DATABASE CHEMCATS 'Online! AsInEx Compound Collection, 10 May 2001 (2001-05-10) Database accession no. 2002:174244 XP002172980 abstract -----	1-12

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		EP 0125204 A	14-11-1984
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		US 5698710 A	16-12-1997